



# ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 12

A. R. Katritzky &  
A. J. Boulton

Advances in  
Heterocyclic  
Chemistry

Volume 12

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Advances in  
**HETEROCYCLIC  
CHEMISTRY**

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## Preface

The twelfth volume of *Advances in Heterocyclic Chemistry* comprises five chapters, four of which deal with the general chemistry of specific groups of heterocyclic compounds; 1,2,3,6-tetrahydropyridines (M. Ferles and J. Pliml), lactim ethers (R. G. Glushkov and V. G. Granik), selenophenes (N. N. Magdesieva), and imidazoles (M. R. Grimmett). The remaining chapter is concerned with the preparative electrolysis of nitrogen heterocycles (H. Lund).

Thanks are due to the Editorial Board, the publisher, and the authors for their cooperation which has enabled us to set a target date of October 1970 for the publication of this volume.

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# Advances in Selenophene Chemistry

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## I. Introduction

Selenophene ( $C_4H_4Se$ ) is a five-membered heterocyclic compound containing one heteroatom. The first compound of this series to be prepared was 2,5-dimethylselenophene, obtained in 1885 by Paal<sup>1</sup> from acetylacetone by heating it with phosphorus pentaselenide. Unsubstituted selenophene was obtained much later; it was mentioned

<sup>1</sup> C. Paal, *Ber.* **18**, 2255 (1885).

by Foa,<sup>2</sup> then reliably described by Mazza and Solazzo<sup>3</sup> in 1927, and, later, by Briscoe,<sup>4,5</sup> and by Sugimoto and Umezawa<sup>6</sup> who obtained it from the reaction of acetylene with selenium.

Although selenophene and certain of its homologs have been known for about 40 years, selenophene chemistry has advanced very slowly, and only a few of the simplest electrophilic substitution reactions of the nucleus were known<sup>7,8</sup> when Yur'ev and his co-workers started their investigations. The development was hindered, probably, because there were no convenient procedures to obtain selenophene, its homologs, and derivatives.

This chapter reviews advances in the chemistry of this hetero-aromatic system over the last 10 or 12 years.

## II. Molecular Structure and Physicochemical Properties of Selenophene

The aromatic  $\pi$ -electron system of selenophene is formed by the interaction of the  $\pi$  electrons of two carbon-carbon double bonds with the lone-pair of the selenium atom. Thus, it contains six electrons in the field of five nuclei; the sixfold symmetry axis characteristic of benzene is removed; there simply remains the plane and one twofold axis, leaving a molecule of  $C_{2v}$  symmetry.<sup>15,23</sup> Therefore, a uniform distribution of electron density is impossible in selenophene. This was confirmed, e.g., by MO calculations of the  $\pi$ -electron structure of the selenophene molecule.

### A. MICROWAVE SPECTRUM

The study of the electronic structure of five-membered heterocycles is considerably assisted by a knowledge of their geometry (Fig. 1).

<sup>2</sup> L. Foa, *Gazz. Chim. Ital.* **39**, 527 (1909).

<sup>3</sup> F. P. Mazza and L. Solazzo, *Rend. Accad. Sci. Fis. Mat. (Soc. Nazl. Sci. Napoli)* **33**, 236 (1927); *Chem. Abstr.* **23**, 2417 (1929).

<sup>4</sup> H. V. A. Briscoe and J. B. Peel, *J. Chem. Soc.*, 1741 (1928).

<sup>5</sup> H. V. A. Briscoe, J. B. Peel, and P. L. Robinson, *J. Chem. Soc.*, 2628 (1928).

<sup>6</sup> H. Sugimoto and S. Umezawa, *Bull. Chem. Soc. Japan* **11**, 157 (1936); *Chem. Abstr.* **30**, 5981 (1936).

<sup>7</sup> S. Umezawa, *Bull. Chem. Soc. Japan* **11**, 775 (1936); *Chem. Abstr.* **31**, 2211 (1937).

<sup>8</sup> S. Umezawa, *Bull. Chem. Soc. Japan* **14**, 155 (1939); *Chem. Abstr.* **33**, 6303 (1939).

There was at one time some uncertainty as to the planarity of the selenophene molecule,<sup>9-12</sup> and the electric moment was also in doubt (0.41 or 0.77 D).<sup>13, 14</sup> Therefore, Pozdeev and others<sup>15</sup> undertook a microwave spectral investigation of selenophene, 2,5-dideuterioselenophene and tetradeuterioselenophene, at  $-40^{\circ}\text{C}$  on spectrographs with Stark modulation (frequency 62.5 or 90 kHz). The sensitivity of the two spectrographs was about  $10^{-9}\text{ cm}^{-1}$ .

The microwave spectra of the three samples showed transitions between lower rotational levels of seventeen molecules of different isotopic compositions. Rotational constants for fifteen of them were determined from eight transitions with  $J \leq 3$ . The rotational constants were obtained on a Ural-3 computer by the least-squares method. For two molecules,  $\alpha\text{-}^{13}\text{C}^{12}\text{C}_3\text{H}_4\text{}^{80}\text{Se}$  and  $\beta\text{-}^{13}\text{C}^{12}\text{C}_3\text{H}_4\text{}^{80}\text{Se}$ , rotation constants

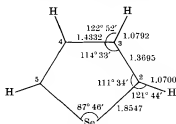


FIG. 1. Bond lengths and angles of the selenophene molecule.

were determined from five transitions with  $J \leq 4$  because transitions with low  $J$  values were not sufficiently intense to measure the constants, due to the low natural abundance of the  $^{13}\text{C}$  isotope. Transitions with higher  $J$  values were not studied because of possible centrifugal perturbation. Table I contains moments of inertia and inertial defects calculated from the rotation constants. The defects verify the planarity of the selenophene molecule. The structure of the selenophene

<sup>9</sup> H. Gerding, G. Milazzo, and H. H. Rossmark, *Rec. Trav. Chim.* **72**, 957 (1953).

<sup>10</sup> M. L. Heffernan and A. Humfray, *Mol. Phys.* **7**, 527 (1964).

<sup>11</sup> M. Nardelli, G. Fova, and G. Giraldi, *Acta Cryst.* **15**, 732 (1962).

<sup>12</sup> A. Trombetti and C. Zauli, *J. Chem. Soc. A*, 1106 (1967).

<sup>13</sup> H. de V. Robles, *Rec. Trav. Chim.* **58**, 111 (1939).

<sup>14</sup> B. Tamamusi, H. Akiyama, and S. Umezawa, *Bull. Chem. Soc. Japan* **14**, 310 (1939); *Chem. Abstr.* **33**, 9064 (1939).

<sup>15</sup> N. M. Pozdeev, O. B. Akulinin, A. A. Shapkin, and N. N. Magdesieva, *Dokl. Akad. Nauk SSSR* **185**, 384 (1969).

molecule was determined by the Kraitchman-Costain method.<sup>16,17</sup> The data in Table I give an overdefined set for the structure, therefore geometry parameters could be independently calculated from the different sets. Thus, the accuracy of the structure obtained can be estimated. The results are shown in Table II. Note that this five-membered ring has the C-Se-C angle less than 90°.

TABLE I

PRINCIPAL MOMENTS OF INERTIA (amu Å<sup>2</sup>), AND INERTIA DEFECTS  $\Delta$   
FOR SEVENTEEN SELENOPHENE MOLECULES OF DIFFERENT ISOTOPIC  
COMPOSITION

Molecule	$I_A$	$I_B$	$I_C$	$\Delta$
C <sub>4</sub> D <sub>4</sub> <sup>76</sup> Se	80.9012	161.2563	242.2383	0.0808
C <sub>4</sub> D <sub>4</sub> <sup>77</sup> Se	80.9066	161.9810	242.9594	0.0718
C <sub>4</sub> D <sub>4</sub> <sup>78</sup> Se	80.9025	162.6921	243.6722	0.0776
C <sub>4</sub> D <sub>4</sub> <sup>80</sup> Se	80.9033	164.0856	245.0670	0.0781
C <sub>4</sub> D <sub>4</sub> <sup>82</sup> Se	80.9000	165.4407	246.4211	0.0804
C <sub>4</sub> α-D <sub>2</sub> H <sub>2</sub> <sup>76</sup> Se	77.4836	147.0603	224.6272	0.0833
C <sub>4</sub> α-D <sub>2</sub> H <sub>2</sub> <sup>77</sup> Se	77.4902	147.7177	225.2828	0.0749
C <sub>4</sub> α-D <sub>2</sub> H <sub>2</sub> <sup>78</sup> Se	77.4873	148.3621	225.9268	0.0774
C <sub>4</sub> α-D <sub>2</sub> H <sub>2</sub> <sup>80</sup> Se	77.4866	149.6254	227.1909	0.0789
C <sub>4</sub> α-D <sub>2</sub> H <sub>2</sub> <sup>82</sup> Se	77.4850	150.8520	228.4184	0.0814
C <sub>4</sub> H <sub>4</sub> <sup>76</sup> Se	66.5319	146.8778	213.4980	0.0883
C <sub>4</sub> H <sub>4</sub> <sup>77</sup> Se	66.5381	147.5271	214.1471	0.0819
C <sub>4</sub> H <sub>4</sub> <sup>78</sup> Se	66.5373	148.1644	214.7846	0.0829
C <sub>4</sub> H <sub>4</sub> <sup>80</sup> Se	66.5327	149.4125	216.0331	0.0879
C <sub>4</sub> H <sub>4</sub> <sup>82</sup> Se	66.5323	150.6244	217.2448	0.0881
α- <sup>13</sup> C <sup>12</sup> C <sub>3</sub> H <sub>4</sub> <sup>80</sup> Se	68.1764	149.7230	217.9809	0.0815
β- <sup>13</sup> C <sup>12</sup> C <sub>3</sub> H <sub>4</sub> <sup>80</sup> Se	67.0272	152.6534	219.7642	0.0836

The molecules C<sub>4</sub>H<sub>4</sub><sup>80</sup>Se, C<sub>4</sub>α-D<sub>2</sub>H<sub>2</sub><sup>80</sup>Se, and C<sub>4</sub>D<sub>4</sub><sup>80</sup>Se were measured for the Stark effect of their 1<sub>01</sub>-2<sub>01</sub> transitions, to give electric dipole moments of 0.368 ± 0.005, 0.392 ± 0.005, and 0.418 ± 0.005 D, respectively.

R. D. Brown,<sup>18</sup> who published simultaneously with Pozdeev,<sup>15</sup> analyzed the microwave spectra of selenophene for two isotopic

<sup>16</sup> J. Kraitchman, *Am. J. Phys.* **21**, 17 (1953).

<sup>17</sup> C. C. Costain, *J. Chem. Phys.* **29**, 864 (1958).

<sup>18</sup> R. D. Brown, F. R. Burden, and P. D. Godfrey, *J. Mol. Spectry.* **25**, 415 (1968).

constitutions of the molecule ( $^{12}\text{C}_4\text{H}_4^{80}\text{Se}$  and  $^{12}\text{C}_4\text{H}_4^{78}\text{Se}$ ), and gave an approximate structure and dipole moment (0.398 D). The structure was obtained by assuming that the corresponding carbon-carbon and carbon-hydrogen bond lengths of thiophene were equal to those of selenophene.

Differences between the length of the C-2-C-3 "double" bond and that of C-3-C-4 are 0.06, 0.05, and 0.07 Å for selenophene, thiophene,<sup>19</sup> and furan,<sup>19</sup> respectively. If bond equivalence is taken as a measure of aromaticity, then the compounds form the following series: furan < selenophene < thiophene.

TABLE II  
GEOMETRIC PARAMETERS OF THE SELENOPHENE MOLECULE

Bond	Lengths (Å)	Angle group	Angles
Se-C-2	$1.8547 \pm 0.0009$	C-5-Se-C-2	$87^\circ 46' \pm 4'$
C-2-C-3	$1.3695 \pm 0.0012$	Se-C-2-C-3	$111^\circ 34' \pm 8'$
C-3-C-4	$1.4332 \pm 0.0030$	C-2-C-3-C-4	$114^\circ 33' \pm 6'$
C-2-H-2	$1.0700 \pm 0.0013$	Se-C-2-H-2	$121^\circ 44' \pm 3'$
C-3-H-3	$1.0792 \pm 0.0011$	C-4-C-3-H-3	$122^\circ 52' \pm 5'$

## B. NMR SPECTRA

Aromatic protons of five-membered heterocyclic systems absorb in the same region as the protons of carbocyclic analogs, namely, 6.9 to 8.5  $\delta$  (1.5–3.1  $\tau$ ). Differences, however, between chemical shifts of the protons located at different positions of the heterocyclic rings are greater than those in benzene derivatives. The differences between the chemical shifts of the  $\alpha$  and  $\beta$  protons in furan, thiophene, and selenophene are 1.05,<sup>20</sup> 0.12,<sup>21</sup> and 0.57 ppm,<sup>20,22</sup> respectively; the difference is least for thiophene, thus confirming its higher aromaticity as compared with furan or selenophene.

<sup>19</sup> B. Back, *Advan. Mol. Spectry*, **1**, 3 (1962).

<sup>20</sup> T. Isobe, *Bull. Chem. Res. Inst. Non-aqueous Solutions, Tohoku Univ.* **9**, 115 (1960).

<sup>21</sup> R. A. Hoffmann and S. Gronowitz, *Arkiv Kemi* **15**, 45 (1960).

<sup>22</sup> N. N. Magdesieva, D.Sc. Thesis, Moscow Univ., 1967.



The NMR spectrum of selenophene (Fig. 2) shows spin-spin interaction of  $^{77}\text{Se}$  with the  $\alpha$  protons, the coupling constant,  $J_{^{77}\text{Se-H}}$  being 22.5 Hz.

Read *et al.*<sup>23</sup> have studied the 60 MHz NMR spectra of selenophene, 2-chloro-, 2-bromo-, 2,5-dichloro-, and 2,5-dibromoselenophene, as well as these compounds containing  $^{13}\text{C}$ . NMR spectra of the thiophene analogs were examined for comparison. The substituent anisotropic effects were estimated and it was shown that five-membered heterocycles are characterized by diamagnetic anisotropy which increases in the series furan < thiophene < selenophene.

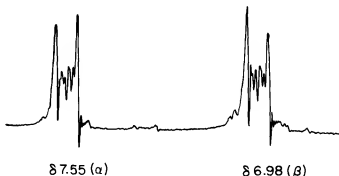


FIG. 2. NMR spectrum<sup>22</sup> of selenophene, taken on JNM-4-H-100 spectrometer at 20°C.

### C. IR AND RAMAN SPECTRA

The vibration spectra of five-membered heteroaromatic systems also give information about their electronic structure, because the positions and intensities of the bands depend on the electron distribution in the molecule.

Gerding *et al.*,<sup>9</sup> who studied the IR and Raman spectra of selenophene, supposed that the molecule was not planar, the selenium atom lying somewhat out of the plane of the four CH groups. Later, several workers disproved this notion.<sup>15</sup> Chumayevskii *et al.*<sup>24</sup> also studied

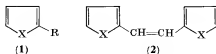
<sup>23</sup> J. Read, C. Mathis, and J. Goldstein, *Spectrochim. Acta* **21**, 85 (1965).

<sup>24</sup> N. A. Chumayevskii, V. M. Tatevskii, and Yu. K. Yur'ev, *Opt. i Spektroskopiya* **6**, 45 (1959); *Chem. Abstr.* **53**, 7764 (1959).

the IR and Raman spectra of selenophene, and of its various mono- and dimethylated homologs. Selenophene showed  $\nu_{\text{CH}}$  bands at 2690 and 3050  $\text{cm}^{-1}$ ; the methyl derivatives absorbed at 2950  $\text{cm}^{-1}$ , and also showed a band due to the methyl group(s) at 2750  $\text{cm}^{-1}$ , its intensity increasing with the number of groups. The ring  $\nu_{\text{C-C}}$  band was reported to be at 1582  $\text{cm}^{-1}$  in selenophene (see Table III).

Other ring vibrations have been reported at frequencies of 1032–1019, 1079–1086, 1358–1349, and 1404–1428  $\text{cm}^{-1}$ , similar to those for thiophene.<sup>9</sup> The  $\nu_{\text{C-Se}}$  frequency lies in the range 700–800  $\text{cm}^{-1}$ . Thus, the IR spectra of selenophene and thiophene are similar in their general shape and the position of their bands, and suggest that the molecules have the same symmetry, i.e.,  $C_{2v}$ .

Yur'ev *et al.*<sup>25</sup> studied the Raman spectra of 2-cyclopropyl-, 2-(2-methylcyclopropyl)-, and 2-(1-propenyl)-selenophene and found ring frequencies similar to those of selenophene and its methyl homologs.<sup>24</sup> On replacement of the *n*-propyl group by cyclopropyl or, particularly, by propenyl, however, the intensities of certain lines increased two- to tenfold, as a result of conjugation.



R =  $n\text{-C}_3\text{H}_7$ -,  $\text{CH}_3\text{CH}=\text{CH}$ -, or cyclopropyl  
 X = O, S, or Se

Treshchova *et al.*<sup>26</sup> studied the Raman spectra of the following furan, thiophene, and selenophene derivatives (1, 2). They found that the intensities of certain bands depend on the number of conjugated double bonds. The integrated intensities of the Raman band for the double bond are 113,000, 300,000, and 800  $\text{mole}^{-1}$  for 1,2-di(fur-2-yl)-, 1,2-di(thien-2-yl)-, and 1,2-di(selenien-2-yl)ethylene (2, X = O, S, or Se, respectively) by reference to the 802  $\text{cm}^{-1}$  band of cyclohexane, the intensity  $J_\infty$  of which is arbitrarily taken as 500  $\text{mole}^{-1}$ .

There is weak conjugation between a three-membered ring and the heterocyclic nucleus. Only a few bands of the cyclopropyl-substituted

<sup>25</sup> Yu. K. Yur'ev, N. N. Magdesieva, and E. G. Treshchova, *Vestn. Mosk. Univ., Ser. II: Khim.* **17**, No. 1, 60 (1962).

<sup>26</sup> E. G. Treshchova, D. Ekkhardt, and Yu. K. Yur'ev, *Zh. Fiz. Khim.* **38**, 295 (1964); *Chem. Abstr.* **60**, 14027 (1964).

TABLE III  
MAIN VIBRATIONS OF THIOPHENE, SELENOPHENE, AND THEIR DEUTERIATED DERIVATIVES

Vibrations*	$C_{2v}$	Thiophenes <sup>b</sup>			Selenophenes <sup>b</sup>			$C_s$	T-2-d	Se-2-d	Se-3-d
		$T_0$	T-2,5-d <sub>2</sub>	T-d <sub>4</sub>	Se <sub>0</sub>	Se-2,5-d <sub>2</sub>	Se-d <sub>4</sub>				
$\nu_1$ CH(D) str.	$A_1$	3110	2325	2333	3100	2318	2335		3107	3095	3099
$\nu_2$ CH(D) str.		3086	3082	2297	3063	3064	2280		3083	3060	3058
$\nu_3$ Ring str.		1408	1390	1372	1419	1409	1398		1398	1410	1411
$\nu_4$ Ring str.		1360	1300	1245	1341	1293	1210		1336	1320	1320
$\nu_5$ CH(D) def. ( $\beta$ )		1081	1042	890	1080	1042	847		1040	1083	1076
$\nu_7$ CH(D) def. ( $\beta$ )		1033	879	780	1010	830	774		902	873	852
$\nu_3$ Ring str.		833	746	728	758	697	683		758	717	739
$\nu_8$ Ring def. ( $\beta$ )		606	588	586	456	446	444	$A'$	598	452	450
$\nu_{12}$ CH(D) str.	$B_1$	3110	2325	2333	3100	2318	2335		2319	2318	3099
$\nu_{13}$ CH(D) str.		3073	3082	2283	3054	3058	2267		3072	3060	2288
$\nu_{14}$ Ring str.		1506	1481	1451	1515	1495	1460		1490	1500	1489
$\nu_{15}$ CH(D) def. ( $\beta$ )		1250	1206	1030	1243	1206	1001		1225	1217	1200
$\nu_{16}$ CH(D) def. ( $\beta$ )		1081	910	840	1080	900	806		1080	1027	1013
$\nu_{17}$ Ring def. ( $\nu, \beta$ )		871	760	772	820	745	718		848	785	810
$\nu_{18}$ Ring def. ( $\beta$ )		750	750	711	623	604	592		748	612	609
$\nu_9$ CH(D) def. ( $\gamma$ )	$A_2$	900	895	756	905	896	748		896	902	894
$\nu_{10}$ CH(D) def. ( $\gamma$ )		686	564	533	685	550	528		568	555	636
$\nu_{11}$ Ring def. ( $\gamma$ )		565	528	488	541	527	475	$A''$	555	537	493
$\nu_{19}$ CH(D) def. ( $\gamma$ )	$B_2$	712	586	533	700	565	520		708	692	680
$\nu_{20}$ CH(D) def. ( $\gamma$ )		864	819	685	870	822	690		839	845	794
$\nu_{21}$ Ring def. ( $\gamma$ )		453	417	411	394	367	362		433	380	387

\* str, stretching ( $\nu$ ); def., deformation (bending);  $\beta$ , in-plane;  $\gamma$ , out-of-plane.

<sup>b</sup> T, thiophene; Se, selenophene; T<sub>0</sub>, Se<sub>0</sub>, undeuteriated rings.

heterocycles have increased intensity in the Raman spectra, compared with the propyl analogs. This also holds for phenylcyclopropanes.<sup>27</sup>

A full interpretation of the vibration spectra of selenophene has been given by Aleksanyan *et al.*,<sup>28, 29</sup> employing a set of deuteriated selenophenes, polarization of the Raman bands, IR band shapes in the gas spectra, crystal IR spectra, and the Brodersen isotopic rule. IR and Raman spectra were recorded (liquid or gas samples) for selenophene and four deuteriated selenophenes (2-*d*-, 3-*d*-, 2,5-*d*<sub>2</sub>, and *d*<sub>4</sub>-selenophene), and IR spectra were recorded of crystals of the symmetric molecules selenophene, 2,5-*d*<sub>2</sub>-selenophene and *d*<sub>4</sub>-selenophene.

To compare the vibration spectra of selenophene with those of thiophene, the latter was similarly investigated together with its deuteriated derivatives.<sup>28, 29</sup>

Thiophene and selenophene have *C*<sub>2v</sub> symmetry, therefore the 21 vibrations of thiophene or selenophene have the following distribution as to the symmetry types:

$$\Gamma = 8A_1 + 3A_2 + 7B_1 + 3B_2$$

For the unsymmetrical deuteriated derivatives (symmetry *C*<sub>s</sub>), this will be:

$$\Gamma = 15A' + 6A''$$

Out-of-plane vibrations of type *B*<sub>2</sub> were assigned based on the fact that they possess depolarized lines in the Raman spectra and bands characterized by band shapes of type C in the IR spectra of the vapor.

Vibrations of type *A*<sub>2</sub> are forbidden in the IR gas-phase spectra, but they may appear in the IR spectra of the crystal if the symmetry of the position in the crystalline lattice is lower than the inherent symmetry of the molecule. X-Ray analysis of thiophene crystals showed that this was possible. Crystalline thiophene, selenophene, and their symmetrical deuteriated derivatives do possess new bands in the IR spectra that correspond to peaks in the Raman but not in the IR gas spectra. These bands were assigned to vibrations of type *A*<sub>2</sub>. Out-of-plane vibrations of type *A*'' obtained with thiophene-2-*d*,

<sup>27</sup> E. G. Treshchova, R. Ya. Levina, Yu. S. Shabarov, and K. S. Shanazarov, *Vestn. Mosk. Univ., Ser. II: Khim.* **12**, No. 5, 145 (1957).

<sup>28</sup> V. T. Aleksanyan, Ya. M. Kimel'fel'd, N. N. Magdesieva, and Yu. K. Yur'ev, *Opt. i Spektroskopiya* **22**, 216 (1967); *Chem. Abstr.* **67**, 48641 (1967).

<sup>29</sup> V. T. Aleksanyan, Ya. M. Kimel'fel'd, N. N. Magdesieva, and Yu. K. Yur'ev, *Opt. Spektroskopiya (Akad. Nauk SSSR, Otd. Fiz.-Mat. Nauk)* **3**, 168, 178 (1967); *Chem. Abstr.* **67**, 86226, 86227 (1967).

selenophene-2-*d*, and selenophene-3-*d* were assigned according to the gas-phase IR spectra (bands of type C) and the Raman spectra (depolarized lines). This assignment satisfies the isotopic product rules and the sum rules. To check the assignment of out-of-plane vibrations of 2-deuteriothiophene and 2-deuterioselenophene, the Brodersen complete isotopic rule was used, which allows each  $A''$  frequency for the two molecules to be calculated from the  $A_2$  and  $B_2$  frequencies of thiophene, 2,5-dideuteriothiophene, selenophene, and 2,5-dideuterioselenophene. The calculated frequencies fit well with the experimental, thus additionally confirming the assignments of  $A_2$  and  $B_2$  frequencies of the more symmetrical molecules.

Vibrations of thiophene, selenophene, and symmetrically deuteriated derivatives of the rings were assigned to the completely symmetric in-plane type  $A_1$ , mainly on Raman evidence (polarized and, as a rule, intense bands). Stretching vibrations of the CH or CD bonds were assigned using empirical regularities in the Raman frequencies and intensities of the CH bands in thiophene, selenophene, and their derivatives. The assignment to vibrations of type  $B_1$  was also made (depolarized bands in the Raman spectra, type B in IR).

Raman spectra of 2-deuteriothiophene, 2-deuterioselenophene, and 3-deuterioselenophene were useful for assigning the vibrations of type  $A'$  because fourteen of the fifteen vibrations of the type are polarized and intense. A deuterium atom distorts the symmetry of the vibrations which are of type  $B'$  in selenophene or thiophene. The assignment of the in-plane vibrations fits the isotopic product rules and the sum rules (see Table III). These data confirm the similarity of the vibrational spectra of thiophene and selenophene.

Assignment of the principal vibrations allowed calculation of the force field of thiophene and selenophene with respect to the symmetry coordinates.<sup>30</sup> The force field factors found for thiophene vibrations of type  $A_1$ ,  $A_2$ , and  $B_2$  were used as the initial approximation for the respective types of selenophene vibrations. The calculated frequencies are in fair agreement with experiment. Therefore, the force field of selenophene is similar to that of thiophene. The  $B_1$  frequencies of selenophene calculated by the force field derived from thiophene disagreed with the experimental values. The differences seem greater than could arise from the uncertainties in the geometry of selenophene.

Later, Trombetti and Zauli<sup>12</sup> studied the IR and Raman spectra

<sup>30</sup> V. T. Aleksanyan, Ya. M. Kimel'fel'd, and N. N. Magdesieva, *Zh. Strukt. Khim.* **9**, 633 (1968); *J. Struct. Chem. USSR* **9**, 550 (1968).

of selenophene and assigned the principal vibrations. Their data fit well those obtained by Aleksanyan *et al.*<sup>28,29</sup> The only discrepancy concerns  $\nu_{20}$  (the frequencies numbered as in Rico *et al.*<sup>31</sup>). Trombetti<sup>12</sup> did not give good reasons for his assignment of the  $793\text{ cm}^{-1}$  band in the IR spectrum to this vibration. The assignment<sup>28</sup> to a weak band at  $870\text{ cm}^{-1}$  is confirmed by strong bands of type C in the IR spectra of deuteriated selenophenes, and also by the application of various isotopic rules.

Kimel'fel'd, Aleksanyan, and Magdesieva<sup>32</sup> studied the substituent effect on the vibrational spectra of furan, thiophene, or selenophene to find criteria to determine the position of a substituent from the Raman frequencies of CH-stretching vibrations. The substituents were bromine, methyl groups, and nitrile groups. The nitrile group was also selected to study the effect of conjugation since its symmetry excludes rotational isomerism. The conjugation of the ring with the substituent caused an increase in the Raman intensity  $\nu_{\text{C}=\text{C}}^s$  and  $\nu_{\text{C}=\text{C}}^a$ . The magnitude of the effect depends on the orientation of the substituent.

#### D. UV SPECTRA

The UV spectra of selenophene and its various mono- and dimethyl homologs were studied by Chumayevskii *et al.*<sup>24</sup> Later, Treshchova *et al.*<sup>26</sup> reported the spectra of the furan, thiophene, and selenophene derivatives (**1**, **2**) with the designated substituents (p. 7). They found that these compounds reveal a conjugation effect, seen in the bathochromic shift of the absorption maxima of their electron spectra, the shifts increasing in the order  $\text{O} < \text{S} < \text{Se}$ .

Italian chemists<sup>33-36</sup> studied the UV spectra of thiophene, selenophene, and a number of their derivatives: (a) with the rings mono-substituted by electron-accepting groups ( $\text{CHO}$ ,  $\text{COOH}$ ,  $\text{COOCH}_3$ , or  $\text{CONH}_2$ )<sup>34</sup> at the 2-position and (b) the disubstituted compounds with bromine<sup>35</sup> or nitro<sup>36</sup> at the 2-position and with the above electron-

<sup>31</sup> M. Rico, J. M. Ozza, and J. Morcillo, *Spectrochim. Acta* **21**, 689 (1965).

<sup>32</sup> Ya. M. Kimel'fel'd, V. T. Aleksanyan, N. N. Magdesieva, and Yu. K. Yur'ev, *Zh. Strukt. Khim.* **7**, 42 (1966); *Chem. Abstr.* **64**, 16859 (1966).

<sup>33</sup> G. Milazzo and E. Miescher, *Gazz. Chim. Ital.* **83**, 782, 787 (1953).

<sup>34</sup> L. Chierici and G. Pappalardo, *Gazz. Chim. Ital.* **88**, 453 (1958).

<sup>35</sup> L. Chierici and G. Pappalardo, *Gazz. Chim. Ital.* **89**, 560 (1959).

<sup>36</sup> A. Bellotti and L. Chierici, *Gazz. Chim. Ital.* **90**, 1125 (1960).

accepting groups at the 5-position. In a comparison of the UV spectra of the monosubstituted isologs<sup>33, 34</sup> no significant difference was found between the electronic effects of the five-membered heterocyclic radicals on the spectral properties of the compounds. The selenophene or thiophene heteroatom lone-pair makes a greater contribution to the  $\pi$  system of the ring than does the lone-pair of furan. The UV spectra of the disubstituted derivatives<sup>35, 36</sup> suggested, however, that the aromaticity of selenophene was somewhat higher than that of thiophene, a result at variance with that provided by NMR spectral evidence (Section II, B).

Trombetti and Zauli<sup>12</sup> studied the UV spectrum of selenophene and showed that selenophene is characterized by absorption at 37,500–47,500  $\text{cm}^{-1}$ , caused by two superimposed transitions.

### III. The Synthesis of Selenophene and Its Homologs

The structure and chemical properties, including syntheses, of selenophene are, in general, similar to those of thiophene.

Selenophene or its homologs are obtained by two main methods: (a) from other heterocycles by the Yur'ev or Perveev procedures, or (b) by ring closure (from 1,4-dicarbonyl compounds, acetylenes, dienes, olefins, or paraffins.)

Yur'ev<sup>37</sup> showed that furan gives selenophene with hydrogen selenide in the presence of magnesium oxide at 450°C.

Perveev *et al.*<sup>38</sup> found that they could obtain alkyl, vinyl, and hydroxyalkyl selenophenes by the reaction of acetylenic  $\alpha$ -epoxides, vinylacetylenic- $\alpha$ -epoxides, or hydroxy- $\alpha$ -epoxides with hydrogen selenide in the presence of barium hydroxide at 20°C. The yield of selenophene (30–80%) depends on the structure of the initial epoxide and decreases with the increase in the chain length or branching.

Yur'ev and Khmel'nitskii<sup>39</sup> developed a synthesis of selenophene and its homologs from the reaction of paraffins, olefins, or conjugated dienes with selenium dioxide in the presence of chromic oxide on alumina at 450°–500°C.

<sup>37</sup> Yu. K. Yur'ev, *Zh. Obshch. Khim.* **16**, 851 (1946); *Chem. Abstr.* **41**, 1654 (1947).

<sup>38</sup> F. Ya. Perveev, N. I. Kudryashova, and D. N. Glebovskii, *Zh. Obshch. Khim.* **26**, 3331 (1956); *Chem. Abstr.* **51**, 9569 (1957).

<sup>39</sup> Yu. K. Yur'ev and L. I. Khmel'nitskii, *Dokl. Akad. Nauk SSSR* **94**, 265 (1954); *Chem. Abstr.* **49**, 3121 (1955).

Arbuzov and Kataev<sup>40</sup> obtained selenophene and its methyl homologs from dienes (butadiene, piperylene, or hexadiene) and metallic selenium at 380°–420°C.

Yur'ev and Magdesieva<sup>41</sup> found a very convenient procedure to obtain selenophene and its homologs by the reaction of butylenes with metallic selenium at 580°C. The selenophene ring closure is most favored when the four-carbon chain of the initial hydrocarbon has a central double bond and the doubly bonded carbons carry as many substituents as possible.

Yur'ev *et al.*<sup>42</sup> prepared deuteriated selenophenes from the respective halogenated compounds by halogen–deuterium replacement. Thus, 2-deuterio-, 2,5-dideuterio-, tetradeuterioselenophene, 3-methyl-, and 5-methyl-2-deuterioselenophene were obtained from the corresponding iodoselenophenes on reduction by zinc in deuteriated acetic acid. 3-Deuterioselenophene was obtained from 3-selenienyllithium hydrolyzed with deuteriated acetic acid at –70°C; the lithium derivative was obtained from 3-bromoselenophene and ethyllithium, also at –70°C. The deuterium content was determined by combustion, the water being analyzed by the drop method.<sup>43</sup>

## IV. Substitution Reactions in the Selenophene Series

### A. ELECTROPHILIC SUBSTITUTION

Selenophene undergoes various electrophilic substitutions: nitration, sulfonation, halogenation, mercuration, chloromethylation, aminomethylation, acylaminomethylation, acylation, formylation, and hydrogen exchange.

#### 1. Nitration

Nitration with fuming nitric acid in acetic anhydride occurs mainly at the  $\alpha$  position, to give 85% 2-nitroselenophene and 15% 3-nitro-

<sup>40</sup> B. A. Arbuzov and E. G. Kataev, *Dokl. Akad. Nauk SSSR*, **96**, 983 (1954); *Chem. Abstr.* **49**, 8907 (1955).

<sup>41</sup> Yu. K. Yur'ev and N. N. Magdesieva, *Sb. IREA (Rept. Inst. Pure Chem. Reagents, USSR)* No. 6, 6 (1962).

<sup>42</sup> Yu. K. Yur'ev, N. N. Magdesieva, and L. Ya. Petrova, *Khim. Geterotsikl. Soedin.* **910** (1966); *Chem. Abstr.* **67**, 11384 (1967).

<sup>43</sup> A. I. Shatenshtein, "Isotope Analysis of Water." USSR Acad. Sci., Moscow, 1957 (in Russian).



selenophene.<sup>44</sup> 2-Nitro- and 3-nitroselenophenes, obtained by decarboxylation of 5-nitro- and 4-nitroselenophene-2-carboxylic acids,<sup>45</sup> respectively, were the reference compounds which proved that Umezawa<sup>7</sup> had nitrated selenophene to obtain a mixture of 2-nitro- (70%) and 3-nitroselenophene (30%) rather than the pure 2-isomer.

2,2'-Diselenienyl,\* obtained by Chierici *et al.*<sup>46</sup> from the reaction of 2-iodoselenophene with activated copper, is nitrated to form the 5,5'-dinitro derivative.

When selenophene-2-aldehyde is nitrated by fuming nitric acid containing sulfuric acid (7%) dissolved in acetic anhydride, the nitro group enters the free  $\alpha'$  position.<sup>47</sup> Nitration by fuming nitric acid and concentrated sulfuric acid, however, gives 4-nitroselenophene-2-aldehyde (45%), 5-nitroselenophene-2-aldehyde (5%), and 2,4-dinitroselenophene (50%). 2,4-Dinitroselenophene probably arises from selenophene-2-carboxylic acid (an oxidation product of selenophene-2-aldehyde); the carboxy group is replaced by nitro to produce 2-nitroselenophene, the subsequent nitration of which leads to 2,4-dinitroselenophene. 2,4-Dinitroselenophene is formed (yield 46%) when selenophene-2-carboxylic acid is nitrated by a mixture of fuming nitric acid and concentrated sulfuric acid.<sup>47</sup> When nitrated by the nitration mixture, 2-acetylselenophene gives products similar to those from selenophene-2-aldehyde, i.e., 4- (50%) and 5-nitro-2-acetylselenophene (8.5%), together with 2,4-dinitroselenophene (41.5%).<sup>45</sup> Here the acetyl group may be at least partially replaced by a nitro group, giving 2-nitro- and, then, 2,4-dinitroselenophene. 5-Nitro-2-acetylselenophene is best obtained by another route, namely, the reaction of 5-nitroselenophene-2-carboxylic acid chloride with ethoxymagnesiummalonic ester followed by hydrolysis and decarboxylation of the product.<sup>48</sup>

\* In this chapter, "selenienyl" is used (analogously to "thienyl" in thiophene chemistry) to denote derivatives of the monosubstituted ring; *Chemical Abstracts* uses "selenophene-yl."

<sup>44</sup> Yu. K. Yur'ev, E. L. Zaitseva, and G. G. Rozantsev, *Zh. Obshch. Khim.* **30**, 2207 (1960); *Chem. Abstr.* **55**, 10416 (1961).

<sup>45</sup> Yu. K. Yur'ev and E. L. Zaitseva, *Zh. Obshch. Khim.* **30**, 859 (1960); *Chem. Abstr.* **55**, 506 (1961).

<sup>46</sup> L. Chierici, C. Dell'Erba, A. Guareschi, and D. Spinelli, *Ric. Sci. A* **8**, 1537 (1958).

<sup>47</sup> Yu. K. Yur'ev and E. L. Zaitseva, *Zh. Obshch. Khim.* **28**, 2164 (1958); *Chem. Abstr.* **53**, 2245 (1959).

<sup>48</sup> Yu. K. Yur'ev and E. L. Zaitseva, *Zh. Obshch. Khim.* **29**, 3644 (1959); *Chem. Abstr.* **54**, 19644 (1960).

Thus, selenophenes are nitrated preferentially at the 2-position unless this position is occupied by an electron-accepting group ( $\text{NO}_2$ ,  $\text{CHO}$ ,  $\text{COCH}_3$ , or  $\text{SO}_2\text{Cl}$ ); then nitration occurs mainly in the 4-position. The free  $\alpha$  position (5-position) is substituted only to about 10–15%.

## 2. Sulfonation

Yur'ev and Sadovaya<sup>49</sup> showed that when selenophene is sulfonated by sulfuric acid<sup>7</sup> or pyridine-sulfur trioxide,<sup>50</sup> the sulfo group enters the 2-position. This was established by the fact that the sulfonic acids so obtained gave sulfonamides identical with those obtained by an independent route (Scheme 1).



SCHEME 1

When selenophene-2-aldehyde or its diacetate is sulfonated with dioxane-sulfur trioxide, 5-sulfoselenophene-2-aldehyde is formed. The 2-carboxylic acid with oleum gives 5-sulfoselenophene-2-carboxylic acid containing an admixture (~20%) of the 4-sulfo isomer. The sulfo group is readily replaced by nitro by the action of fuming nitric acid.<sup>51</sup>

Thus, sulfonation of the selenophene containing an electron-accepting substituent ( $\text{CHO}$  or  $\text{COOH}$ ) is influenced more strongly by the heteroatom than by the carboxyl or carbonyl, and the sulfo group is directed mainly to the free  $\alpha$  position.

## 3. Halogenation

Bromo and chloro derivatives of selenophene are obtained by direct halogenation, whereas iodo derivatives are obtained either

<sup>49</sup> Yu. K. Yur'ev and N. K. Sadovaya, *Zh. Obshch. Khim.* **34**, 1803 (1964); *Chem. Abstr.* **61**, 8258 (1964).

<sup>50</sup> E. G. Kataev and A. E. Zimkin, *Uch. Zap., Kazansk. Gos. Univ.* **117**, 174 (1957).

<sup>51</sup> Yu. K. Yur'ev and N. K. Sadovaya, *Zh. Obshch. Khim.* **34**, 2190 (1964); *Chem. Abstr.* **61**, 9454 (1964).

through exchange of  $\text{HgX}$  for iodine or by iodination by iodine in the presence of yellow mercuric oxide.

When chlorinated at  $50^{\circ}$ – $60^{\circ}\text{C}$ , selenophene gives a mixture of 2-chloro- and 2,5-dichloroselenophene; an excess of chlorine results in addition and substitution, leading to hexachloroselenolane, whereas chlorination in carbon disulfide at  $-15^{\circ}\text{C}$  produces tetrachloroselenolane.<sup>5</sup> Chlorination with sulfuryl chloride yields only the monochloroselenophene.<sup>52</sup> Tetrachloroselenophene is formed from the reaction of selenium with an equimolar amount of hexachlorobutadiene at  $250^{\circ}\text{C}$ ; this is a new method for synthesizing chlorinated selenophenes.<sup>53</sup>

Bromination in carbon disulfide at  $-20^{\circ}\text{C}$  converts selenophene into 2-bromoselenophene; excess of bromine leads to 2,5-dibromo- and 2,3,5-tribromoselenophene.<sup>6</sup>

Iodine in the presence of yellow mercuric oxide converts selenophene, 3-methyl-, 2,4-dimethyl-, and 3,4-dimethylselenophene into the respective  $\alpha$ -monoiodo derivatives.<sup>54</sup> If a  $\beta$ -position of the nucleus is occupied by an electron-donating substituent (methyl group), then the compound is iodinated in the adjacent  $\alpha$  position.<sup>55</sup>

No  $\beta$ -monohalogenated selenophenes are obtained by direct halogenation.  $\beta$ -Bromoselenophene is readily obtained from 2,3,5-tribromoselenophene by debromination with zinc in acetic acid; this procedure is based on the different debromination (metallation) rates of  $\alpha$ - and  $\beta$ -bromoselenophenes.<sup>56</sup>

Selenophene-2-aldehyde and its diacetate are halogenated at the free  $\alpha$  position of the selenophene ring; when treated with nitric acid, the haloaldehyde readily exchanges its bromine for a nitro group.<sup>52</sup>

Thus, halogen also enters the  $\alpha$  position of the ring and even when an electron-accepting substituent occupies one  $\alpha$  position, the halogen enters the free  $\alpha'$  position.

<sup>52</sup> Yu. K. Yur'ev, N. N. Mezentsova, and A. T. Monakhova, *Zh. Obshch. Khim.* **30**, 2726 (1960); *Chem. Abstr.* **55**, 15459 (1961).

<sup>53</sup> W. Mack, *Angew. Chem.* **77**, 260 (1965).

<sup>54</sup> Yu. K. Yur'ev and N. K. Sadovaya, *Zh. Obshch. Khim.* **26**, 3154 (1956); *Chem. Abstr.* **51**, 8712 (1957).

<sup>55</sup> Yu. K. Yur'ev, N. K. Sadovaya, and M. A. Gal'bershtam, *Zh. Obshch. Khim.* **28**, 620 (1958); *Chem. Abstr.* **52**, 17234 (1958).

<sup>56</sup> Yu. K. Yur'ev, N. K. Sadovaya, and E. A. Grekova, *Zh. Obshch. Khim.* **34**, 847 (1964); *Chem. Abstr.* **60**, 15817 (1964).

#### 4. Mercuration

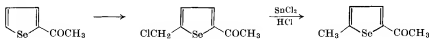
The selenophene nucleus is readily mercured by mercuric salts, the HgX group entering the 2-position.<sup>57, 58</sup> 2-Bromo-, 2-acetyl-, 2-carbethoxy-, and 2-nitroselenophenes are mercured at the 5-position.<sup>59</sup>

#### 5. Chloromethylation

Chloromethylation of selenophene, like other electrophilic substitutions, occurs at the  $\alpha$  position, and 2-chloromethylselenophene is formed together with small amounts of the 2,5-bischloromethyl derivative. Selenophene and its homologs have been chloromethylated by diverse reagents: formalin and hydrogen chloride, a mixture of mono- and bischloromethyl ether, or formaldehyde bischloromethylacetal. A mixture of mono- and bischloromethyl ether is the most convenient reagent.

Catalysts ( $\text{ZnCl}_2$ ,  $\text{SnCl}_2$ ,  $\text{H}_3\text{PO}_4$ , or  $\text{POCl}_3$ ) sharply decrease the reaction yield. Methyl selenophenes are chloromethylated under milder conditions than the unsubstituted compound, and 3-methylselenophene is chloromethylated easier than the 2-methyl compound.<sup>60</sup>

Acyl selenophenes are chloromethylated at the free  $\alpha$  position (as in sulfonation and halogenation). A second chloromethyl group can be introduced "ortho" to the first and "meta" to the acyl group.<sup>61</sup> 5-Methyl-2-acetylselenophene is chloromethylated in the 4-position.<sup>61</sup> When reduced by stannous chloride in hydrochloric acid, 5-chloromethyl-2-acetylselenophene simply undergoes reduction of the chloromethyl group, and 2-methyl-5-acetylselenophene is formed<sup>61</sup> (Scheme 2).



SCHEME 2

<sup>57</sup> Yu. K. Yur'ev, N. K. Sadovaya, and M. A. Gal'bershtam, *Zh. Obshch. Khim.* **29**, 1970 (1959); *Chem. Abstr.* **54**, 8777 (1964).

<sup>58</sup> M. T. Bogert and C. N. Andersen, *J. Am. Chem. Soc.* **48**, 223 (1926).

<sup>59</sup> Yu. K. Yur'ev, M. A. Gal'bershtam, and L. L. Kandror, *Khim. Geterotsikl. Soedin.* 897 (1966); *Chem. Abstr.* **66**, 94453 (1967).

<sup>60</sup> Yu. K. Yur'ev, N. K. Sadovaya, and M. A. Gal'bershtam, *Zh. Obshch. Khim.* **32**, 259 (1962); *Chem. Abstr.* **57**, 16535 (1962).

<sup>61</sup> Yu. K. Yur'ev, N. K. Sadovaya, and E. N. Lyubimova, *Zh. Obshch. Khim.* **30**, 2732 (1960); *Chem. Abstr.* **55**, 15460 (1961).

### 6. Aminomethylation

Selenophene and its homologs are dialkylaminomethylated by dimethylamine hydrochloride and paraformaldehyde in anhydrous alcohol;<sup>62</sup> the reaction gives hydrochlorides of the respective  $\alpha$ -(*N*-dimethylaminomethyl)selenophenes.

*N*-Unsubstituted  $\alpha$ -aminomethylselenophenes are formed when ammonium chloride and 30% formalin are used for the aminomethylation. 3-Methylselenophene is aminomethylated at the 2-position.<sup>62</sup>

### 7. Acylaminomethylation

The selenophene ring is acylaminomethylated only by methylolbenzamide (*N*-benzoylhydroxymethylamine) in the presence of 85% phosphoric acid, and this reaction gives a di-*N*-benzoyl derivative of bisaminomethylselenophene.<sup>62</sup> The formation of a disubstituted derivative may be caused by the fact that the first *N*-benzoylamino-methyl group in the  $\alpha$  position strongly activates the selenophene ring.

When benzoylamino-methylated under these conditions, 2-methylselenophene gives a mixture of mono- and di-(*N*-benzoylamino-methyl) derivatives. If both  $\alpha$  positions of the selenophene ring are already occupied, then the nucleus is substituted at the 3- and 4-positions.

### 8. Acylation

The selenophene ring may be acylated by acyl chlorides under Friedel-Crafts conditions<sup>7, 63</sup> by acid anhydrides in the presence of 85% phosphoric acid<sup>64</sup> and by organic silicoanhydrides (tetraacyloxysilanes) in the presence of stannic chloride.<sup>65-67</sup> When acylated by silicoanhydrides of dibasic organic acids (succinic, adipic, azelaic, or

<sup>62</sup> Yu. K. Yur'ev, N. K. Sadovaya, and A. B. Ibragimova, *Zh. Obshch. Khim.* **29**, 3647 (1959); *Chem. Abstr.* **54**, 19644 (1960).

<sup>63</sup> N. P. Buu-Hoi, P. Demerseman, and R. Royer, *Compt. Rend.* **237**, 397 (1953).

<sup>64</sup> E. G. Kataev and M. V. Palkina, *Uch. Zap., Kazansk. Gos. Univ.* **113**, 115 (1953); *Chem. Abstr.* **50**, 937 (1956).

<sup>65</sup> Yu. K. Yur'ev and G. B. Elyakov, *Dokl. Akad. Nauk SSSR* **102**, 763 (1955); *Chem. Abstr.* **50**, 4796 (1956).

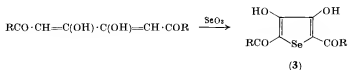
<sup>66</sup> Yu. K. Yur'ev and N. K. Sadovaya, *Zh. Obshch. Khim.* **26**, 930 (1956); *Chem. Abstr.* **50**, 14706 (1956).

<sup>67</sup> Yu. K. Yur'ev, N. K. Sadovaya, and V. V. Titov, *Zh. Obshch. Khim.* **28**, 3036 (1958); *Chem. Abstr.* **53**, 9182 (1959).

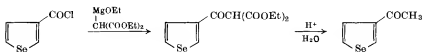
sebacic) or by acid esters of the acids in the presence of anhydrous tin dichloride, selenophene is converted into the respective keto acids.<sup>68</sup>

Thus, ketones of the selenophenes series are most readily obtained from selenophene by acylation with either tetraacyloxysilanes or acid anhydrides, the acyl group always entering the  $\alpha$  position of the ring.

No diacylated selenophene can be obtained by direct acylation; however, 2,5-diacyl-3,4-dihydroxyselenophenes (**3**) were obtained from 1,3,4,6-tetraketones and selenium dioxide in dioxane.<sup>69</sup>



Since acylation of the selenophene nucleus failed to produce  $\beta$ -acylated selenophenes, 3-acetylselenophene is synthesized from the corresponding acid chloride (Scheme 3).<sup>56</sup>



SCHEME 3

Acylation of 2,2'-diselenienyl gives the 5,5'-diacetyl derivative.<sup>46</sup>

### 9. Formylation

Selenophene and its homologs are easily formylated by dimethylformamide in the presence of phosphorus oxychloride; as usual the formyl group always enters the  $\alpha$  position.<sup>70</sup> Methyl selenophenes are formylated under milder conditions than is the unsubstituted selenophene.<sup>71</sup> 2-Methylselenophene gives the 5-formyl,<sup>71</sup> and 3-methylselenophene the 2-formyl derivative.<sup>55</sup>

<sup>68</sup> Yu. K. Yur'ev, G. B. Elyakov, and Z. V. Belyakova, *Zh. Obshch. Khim.* **26**, 2353 (1956); *Chem. Abstr.* **51**, 5037 (1957).

<sup>69</sup> K. Balenovic, D. Cerar, and L. Filipovic, *J. Org. Chem.* **19**, 1556 (1954).

<sup>70</sup> Yu. K. Yur'ev and N. N. Mezentsova, *Zh. Obshch. Khim.* **27**, 179 (1957); *Chem. Abstr.* **51**, 12878 (1957).

<sup>71</sup> Yu. K. Yur'ev, N. N. Mezentsova, and V. E. Vas'kovskii, *Zh. Obshch. Khim.* **27**, 3155 (1957); *Chem. Abstr.* **52**, 9065 (1958).

5-Halogenated selenophene-2-aldehydes may be obtained either from selenophene-2-aldehyde halogenated (chlorinated or brominated) by the respective *N*-halosuccinimide<sup>72</sup> or by formylation of the 2-halo-selenophenes.<sup>72, 73</sup>

Selenophene-3-aldehyde has been obtained by the Sommelet reaction of 3-bromomethylselenophene (obtained from 3-methylselenophene and *N*-bromosuccinimide), by reaction of dimethylformamide with 3-lithioselenophene (obtained by lithium-iodine exchange at  $-60^{\circ}\text{C}$ ),<sup>74</sup> and by reduction and subsequent hydrolysis of selenophene-3-carbonitrile.<sup>75</sup>

2,5-Dimethyl-3-formylselenophene was obtained by the Sommelet reaction on 2,5-dimethyl-3-chloromethylselenophene.<sup>60</sup> 2,5-Diformylselenophene has been prepared in two ways: reaction of dimethylformamide with 2-lithio-5-formylselenophene (obtained from 2-formylselenophene and butyllithium) and hydrolysis of the nitrone from the reaction of *p*-nitrosodimethylaniline with the pyridinium salt obtained from 2,5-bischloromethylselenophene.<sup>76</sup>

Thus, selenophene has been shown in various electrophilic substitution reactions to be a typically aromatic system similar to thiophene. In both systems, all electrophilic substitutions lead, predominantly or exclusively, to the formation of  $\alpha$ -substituted products. If an  $\alpha$  position of the selenophene ring is occupied by a group, whether electron-accepting or electron-donating, electrophilic substitution proceeds predominantly or exclusively at the free  $\alpha'$  position, and so the orientation is principally directed by the heteroatom, rather than by the substituent. When an electron-donating substituent is attached to a  $\beta$  position, substitution proceeds at the adjacent  $\alpha$  position, as expected.

All these regularities, however, only allow a qualitative comparison of selenophene with thiophene. For a quantitative comparison of the two systems, which is necessary for a better understanding of the influence of the heteroatom on the reactivity of the system, results from kinetic experiments must be obtained.

<sup>72</sup> Yu. K. Yur'ev, N. N. Mezentsova, and A. T. Monakhova, *Zh. Obshch. Khim.* **30**, 2726 (1960); *Chem. Abstr.* **55**, 15459 (1961).

<sup>73</sup> L. Chierici and G. Pappalardo, *Gazz. Chim. Ital.* **89**, 560 (1959).

<sup>74</sup> C. Paulmier and P. Pastour, *Compt. Rend.* **C265**, 926 (1967).

<sup>75</sup> Yu. K. Yur'ev, N. N. Magdesieva, and A. T. Monakhova, *Khim. Geterotsikl. Soedin.* **649** (1968).

<sup>76</sup> C. Paulmier and P. Pastour, *Bull. Soc. Chim. France*, 4021 (1966).

The electrophilic aromatic substitution reaction may be advantageously modeled by isotopic exchange reactions. Shatenshtein and his co-workers<sup>77-79</sup> studied hydrogen exchange catalyzed by acids and bases in nonaqueous solution, and their studies throw considerable light on both electrophilic substitution and protophilic (base-induced) replacement of hydrogen in the system (see Section V, A).

TABLE IV  
RATE CONSTANTS AND PARTIAL RATE FACTORS FOR DEUTERIUM EXCHANGE  
AT 25°C<sup>79,84</sup>

Compound	$k$ (sec <sup>-1</sup> )	$f$
Acidic medium (4:1 CH <sub>3</sub> COOH/CF <sub>3</sub> COOH)		
2-Deuterioselenophene	$5.5 \times 10^{-6}$	1
3-Methyl-2-deuterioselenophene	$1.3 \times 10^{-3}$	236
5-Methyl-2-deuterioselenophene	$5.9 \times 10^{-4}$	107
Alkaline medium (C <sub>4</sub> H <sub>9</sub> OLi in DMSO)		
2-Deuterioselenophene	$1.5 \times 10^{-4}$	1
3-Deuterioselenophene <sup>a</sup>	$1.0 \times 10^{-4}$	$2.5 \times 10^{-5}$
3-Methyl-2-deuterioselenophene	$7.7 \times 10^{-6}$	0.05
5-Methyl-2-deuterioselenophene	$1.8 \times 10^{-5}$	0.12
(C <sub>4</sub> H <sub>9</sub> OK in 70% C <sub>4</sub> H <sub>9</sub> OH and 30% diglyme)		
2-Deuterioselenophene	$2.1 \times 10^{-5}$	1
3-Methyl-2-deuterioselenophene	$4.1 \times 10^{-6}$	0.19
5-Methyl-2-deuterioselenophene	$5.8 \times 10^{-6}$	0.27

<sup>a</sup> 50°C, C<sub>4</sub>H<sub>9</sub>OK. The calculation of  $f$  assumes that the isotope exchange catalyzed potassium *t*-butoxide proceeds 2600 times faster than that catalyzed by lithium *t*-butoxide and that the reaction becomes tenfold faster on increasing the temperature by 25°C.

#### 10. Isotopic Exchange of Deuterioselenophenes with Acids

Electrophilic hydrogen exchange in deuterioselenophenes was studied using a 4:1 mixture of acetic and trifluoroacetic acids.<sup>79</sup> Rate constants and partial rate factors were determined for the deuterium replacement at 25°C (see Table IV). Rate constants were calculated

<sup>77</sup> A. I. Shatenshtein, "Isotopic Exchange and Hydrogen Substitution in Organic Compounds." USSR Acad. Sci., Moscow, 1960 (in Russian).

<sup>78</sup> A. I. Shatenshtein, *Tetrahedron* **18**, 95 (1962).

<sup>79</sup> A. I. Shatenshtein, N. N. Magdesieva, Yu. I. Ranneva, I. O. Shapiro, and A. I. Serebryanskaya, *Teor. Eksp. Khim.* **3**, 343 (1967); *Chem. Abstr.* **68**, 58799 (1968).



from the first-order kinetics of the exchange reaction for various selenophenes (2-deuterio-, 2-deuterio-5-methyl-, and 2-deuterio-3-methylselenophene). The results allow quantitative estimates of the reactivity dependence on the ring position and on the presence of electron-accepting substituents. Selenophene is rather unstable toward acids, and therefore attempts at electrophilic dedeuteriation at the 3-position failed to give a rate constant. A methyl group, which displays  $+I$  and  $+M$  effects, accelerated the acid-catalyzed deuterium exchange at the 2-position, the acceleration being more pronounced when the methyl group is attached to the 3-position of the ring.

## B. OTHER NUCLEAR SUBSTITUTION REACTIONS

### 1. Metallation

Selenophene and its homologs are readily metallated (hydrogen-metal exchange) by organolithium compounds, whereby an  $\alpha$ -hydrogen is replaced.<sup>56</sup> Halogen-metal exchange readily occurs with 2-iodoselenophene, which was metallated by phenyllithium<sup>54</sup> and by magnesium<sup>80, 81</sup> to give organometallic derivatives the carboxylation of which produced selenophene-2-carboxylic acid. With benzophenone,  $\alpha$ -selenienylmagnesium bromide gives diphenyl- $\alpha$ -selenienylcarbinol.<sup>81</sup>

Metallation followed by carbonation of 3-bromoselenophene yields, depending on the reagents and temperature,<sup>56</sup> either 3-bromoselenophene-2-carboxylic acid (phenyllithium, 36°C) or selenophene-3-carboxylic acid (butyllithium, -50°C). When treated with butyllithium, the acetal of selenophene-2-aldehyde is metallated at the free  $\alpha'$  position; subsequent carboxylation leads to 2-formylselenophene-5-carboxylic acid.<sup>76</sup>

The experimental evidence thus indicates that selenophene is metallated in much the same manner as thiophene.<sup>82, 83</sup>

<sup>80</sup> Yu. K. Yur'ev and N. K. Sadovaya, *Zh. Obshch. Khim.* **28**, 2162 (1958); *Chem. Abstr.* **53**, 2245 (1959).

<sup>81</sup> A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1389 (1957); *Chem. Abstr.* **52**, 7269 (1958).

<sup>82</sup> S. Gronowitz, *Arkiv Kemi* **7**, 361 (1954).

<sup>83</sup> S. Gronowitz and K. Halvarson, *Arkiv Kemi* **8**, 343 (1955).

## 2. Base-Catalyzed Hydrogen Exchange

Deuteriated selenophenes (2-deuterio, 3-deuterio, 2-deuterio-3-methyl, and 2-deuterio-5-methyl) underwent isotopic exchange in dimethyl sulfoxide containing 0.4 *M* lithium butoxide catalyst at 25°C or 0.5 *M* potassium *t*-butoxide at 50°C (in the case of deuterium exchange in 3-deuterioselenophene); the reaction proceeds by a protophilic mechanism.<sup>79,84</sup> Rate constants and partial rate factors were determined from the pseudo first-order kinetics of the dedeuteriation. Since chemical reactivity, as illustrated by deuterium exchange, in dimethyl sulfoxide solution is known<sup>85</sup> to differ sharply from that found in other solvents, similar measurements were carried out in a mixture (7:3 v/v) of *t*-butanol and diethylene glycol dimethyl ether (diglyme) containing 0.8 *M* potassium *t*-butoxide.

Protophilic exchange of deuterium proceeds 50,000 times faster at an  $\alpha$  than at a  $\beta$  position of selenophene. An electron-donating methyl group hinders the exchange, and this effect is most pronounced in 2-deuterio-3-methylselenophene.

The kinetic results are shown in Table IV, with the results of acid-catalyzed exchange for comparison.

## V. The Reactivity of Selenophene Compared with Thiophene and Furan

### A. SUBSTITUTIONS AT THE NUCLEUS

Isotope exchange is a technique which gives reliable comparative data on the electrophilic and protophilic reactivity of the five-membered heterocycles furan, thiophene, and selenophene, revealing how the activity of their hydrogen atoms varies with the position of the hydrogen in the ring and with the number and position of substituents. The results from kinetic data on isotopic exchange in deuterated selenophenes, thiophenes, and furans, may be summarized as follows.

1. When treated with lithium *t*-butoxide in DMSO, selenophene<sup>79, 84</sup> exchanges  $\alpha$ -deuterium atoms approximately 1.5 times faster than

<sup>84</sup> A. I. Shatenshtein, I. O. Shapiro, Yu. I. Ranneva, N. N. Magdesieva, and Yu. K. Yur'ev, *Reaktsionnaya Sposobnost Org. Soedin., Tartusk. Gos. Univ.* **1**, 236 (1964); *Chem. Abstr.* **62**, 8460 (1965).

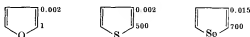
<sup>85</sup> A. I. Shatenshtein, I. O. Shapiro, F. S. Yakushin, G. G. Isaeva, and Yu. I. Ranneva, *Kinetika i Kataliz* **5**, 752 (1964); *Chem. Abstr.* **61**, 15949 (1964).

thiophene<sup>86</sup> and 700 times faster than furan. This may be explained by the fact that selenium is more efficient than sulfur at stabilizing the carbanion transition state through the contribution of its empty *d* orbitals.

2. Potassium *t*-butoxide in DMSO causes  $\beta$ -deuterium exchange eight times faster in selenophene than in thiophene. The  $\beta$  atoms are exchanged as fast in thiophene as in furan under these conditions.<sup>86</sup> This may be explained assuming that the lone-pair of the selenium heteroatom is more strongly conjugated with the  $\pi$  electrons of the ring than is that of the sulfur.

3. The protophilic exchange rate for  $\alpha$ -deuterium atoms differs from that for  $\beta$  atoms by a factor of 50,000 in selenophene, 250,000 in thiophene, and 500 in furan.

The structures below summarize hydrogen activities of selenophene, thiophene, and furan in protophilic isotope exchange; the rate constant of deuterium exchange at the  $\alpha$  position of furan is arbitrarily given the value of unity.



4. In an acidic medium,  $\alpha$ -deuterium atoms in selenophene<sup>79</sup> are exchanged approximately six to ten times faster than those in thiophene.<sup>86</sup>

5. A methyl group, which displays electron-donor properties (+*I*, +*M*), facilitates the acid-catalyzed and hinders the alkali-catalyzed exchange, in deuteriated methylselenophenes. The partial rate factors (*f*) show that a methyl group transfers its electronic effect in selenophene<sup>79</sup> almost as effectively as in thiophene.<sup>86</sup>

6. The positive inductive effect of a 3-methyl group is transferred to the adjacent 2-position more effectively than that of a 2-methyl to the more remote 5-position. Compared with the rate of  $\alpha$ -deuterium exchange for selenophene, itself, the rate is about 0.1 for 5-methyl-2-deuterioselenophene and 0.05 for 3-methyl-2-deuterioselenophene in the presence of strong bases, whereas in acidic media it is about 100 and 1000, respectively.<sup>79</sup> The same effect of a methyl group was found

<sup>86</sup> A. I. Shatenshtein, A. G. Kamrad, I. O. Shapiro, Yu. I. Ranneva, and E. N. Zvyagintseva, *Dokl. Akad. Nauk SSSR* **168**, 364 (1966); *Chem. Abstr.* **65**, 8695 (1966).

in the reactivity of the deuterium atoms of 5-methyl-2-deuterio- and 3-methyl-2-deuteriothiophenes in acidic and strongly alkaline media.<sup>86</sup>

7. Partial rate factors ( $f$ ) obtained from deuterium exchange in 2-deuteriated 3- and 5-methylselenophenes and thiophenes were compared with the  $f$  values of deuterium exchange in *o*-, *m*-, and *p*-deuteriated toluenes<sup>87, 88</sup>; the comparison shows that the acid- and base-catalyzed exchange of deuterium is similarly affected by methyl substituents in the selenophene, thiophene, and benzene series. Hence, the heterocycles behave here as normal aromatic systems.

A second quantitative comparison of the reactivity of selenophene with that of thiophene is by the kinetics of mercuration (at the 5-position) of 2-substituted derivatives of the two series. It was found that 2-bromo-, 2-acetyl-, 2-carbethoxy-, and 2-nitroselenophenes<sup>89</sup> are mercured 1.5 to 3 times faster than the corresponding derivatives of thiophene.<sup>89</sup> The substituent effects for selenophenes follow the Hammett equation using  $\sigma^+$  values.

Selenophene compounds are also more reactive in nucleophilic substitutions. Thus, 3-nitro- and 5-nitro-2-bromoselenophenes<sup>90</sup> react with piperidine faster than do the corresponding thiophenes.<sup>91</sup> The effect of electron-accepting substituents on the nucleophilic substitution of bromine located at the 2-position of 3,5-disubstituted selenophenes has been studied, as also has the applicability of the Hammett equation to this piperidino-debromination.<sup>92</sup>

Thus, the kinetic results show that selenophene undergoes both electrophilic and nucleophilic substitution reactions somewhat more readily than does thiophene. Hence, the reactivity of the heterocycle increases when sulfur is replaced by selenium; a possible explanation might be that the selenium atom is larger and more polarizable, and therefore more willing both to release its *p* electrons and to accept electrons into its free *d* orbitals.

<sup>87</sup> W. M. Lauer and G. Stedman, *J. Am. Chem. Soc.* **80**, 6439 (1958).

<sup>88</sup> E. N. Yurygina, P. P. Alikhanov, E. A. Izrailevich, P. N. Manochkina, and A. I. Shatenshtein, *Zh. Fiz. Khim.* **34**, 587 (1960); *Chem. Abstr.* **55**, 17548 (1961).

<sup>89</sup> R. Motoyama, S. Nishimura, E. Imoto, and Y. Murakami, *Nippon Kagaku Zasshi* **78**, 962 (1957); *Chem. Abstr.* **54**, 14224 (1960).

<sup>90</sup> L. Chierici, C. Dell'Erba, A. Guareschi, and D. Spinelli, *Ann. Chim. (Rome)* **57**, 632 (1967).

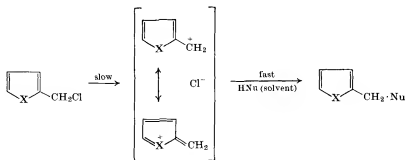
<sup>91</sup> C. Dell'Erba and D. Spinelli, *Tetrahedron* **21**, 1061 (1965).

<sup>92</sup> C. Dell'Erba, A. Guareschi, and D. Spinelli, *J. Heterocycl. Chem.* **4**, 438 (1967).

## B. SOLVOLYSIS OF CHLOROMETHYL DERIVATIVES

Based on solvolysis kinetics, the reactivity of chlorine in chloromethylated selenophenes has been quantitatively compared with that in the derivatives of thiophene and furan.<sup>93</sup>

The solvolysis proceeds by the unimolecular ( $S_N1$ ) mechanism:



The compounds are solvolyzed some  $10^4$  times faster than benzyl chloride in methanol. Hence, the furan, thiophene, and selenophene rings are more efficient than the phenyl at stabilizing a positive charge at an  $\alpha$  carbon.

3-Chloromethyl-2,5-dimethyl derivatives of furan, thiophene, and selenophene are solvolyzed faster than their 2-chloromethyl derivatives. For both the 2-chloromethyl and the 3-chloromethyl-3,5-dimethyl series the solvolysis rate increases in the order thiophene < selenophene < furan.

The Hammett equation, using  $\sigma^+$  parameters, correlates well the effect of substituents at the 5-position on the solvolysis rate of 5-chloro-, 5-bromo-, 5-nitro-, and 5-acetyl-2-chloromethylselenophenes, with a  $\rho$  value of  $-6.42$ . The very large negative  $\rho$  value once more reflects the somewhat higher polarizability of selenophene than thiophene.

<sup>93</sup> Yu. K. Yur'ev, M. A. Gal'bershtam, and A. F. Prokof'eva, *Izv. Vysshikh. Uchebn. Zavedenii SSSR, Khim. i Khim. Tekhnol.* **7**, 419, 598 (1964), **8**, 421 (1965); *Chem. Abstr.* **61**, 13149 (1964), **62**, 3897 (1965), **63**, 16151 (1965).

## C. COMPARISON BETWEEN FURAN, THIOPHENE, AND SELENOPHENE FROM OTHER PROPERTIES AND REACTIONS

The "aromaticity" of a heterocycle depends on how effectively the lone-pair of the heteroatom contributes to the aromatic sextet. The aromaticity of five-membered heterocyclic compounds may be estimated from their reactivity in the Diels-Alder reaction.<sup>94</sup> Spectrophotometry shows that furan, thiophene, and selenophene resemble benzene in that with maleic anhydride 1:1 complexes are formed which are stable up to 150°C in the case of thiophene, decompose at 150°C with selenophene (whereby selenium is formed together with a diene which gives a further adduct with another molecule of maleic anhydride), and produce the usual adduct at 20°C with furan. Thus, only furan is a normal diene as regards the Diels-Alder reaction.

Pauling electronegativities<sup>95</sup> are 3.5, 2.5, and 2.4 for O, S, and Se, respectively; therefore the oxygen in furan releases its electron pair to the aromatic sextet less effectively than the sulfur in thiophene, and the latter less than the selenium of selenophene. Thus, the  $\pi$ -electron density localized at the heteroatom decreases in the series: furan > thiophene > selenophene.

Polarographic reduction of a nitro group at the 2-position showed<sup>96</sup> that 2-nitrofuran was the easiest to reduce, while 2-nitrothiophene and 2-nitroselenophene required 20–30 mV, and nitrobenzene 40 mV higher potential. The reduction potentials of the five-membered heterocyclic isologs may increase with a decrease in electron shifts produced by the lone-pair of the heteroatom in the series: O > S > Se. Hence, in its polarographic behavior 2-nitroselenophene is closer to nitrobenzene than to nitrofuran.

The basicities of 3,5-disubstituted pyrazoles carrying a heterocyclic substituent ( $\alpha$ -furyl,  $\alpha$ -thienyl,  $\alpha$ -selenienyl) (4) were all less than that of the unsubstituted pyrazole and fall into the order indicated; hence all the above heterocyclic groups are electron-acceptors with respect to hydrogen for the pyrazole ring.<sup>97</sup> Pyrazole, when substituted as

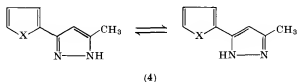
<sup>94</sup> B. A. Arbuzov and A. I. Konovalov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2130 (1959); *Chem. Abstr.* **54**, 10813 (1960).

<sup>95</sup> L. Pauling, *J. Am. Chem. Soc.* **54**, 3570 (1932).

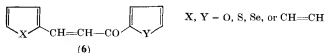
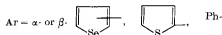
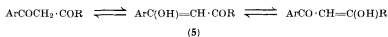
<sup>96</sup> J. Stradins, S. Hillers, and Yu. K. Yur'ev, *Dokl. Akad. Nauk SSSR* **129**, 816 (1959); *Chem. Abstr.* **54**, 6363 (1960).

<sup>97</sup> I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.* **32**, 3025 (1962); *Chem. Abstr.* **58**, 8881 (1963).

above, suffers a bathochromic shift of its UV maximum by 25 to 50 m $\mu$ , and the magnitude of the shift depends on the substituent in the same way as the basicity does; in other words, it depends on the substituent-to-nucleus conjugation.



The electronic effects of the thienyl and selenienyl radicals can also be compared by examining the enolization of  $\beta$ -diketones (5).<sup>75, 98, 99</sup> In these systems the percentage of enolic form increases along the series:  $\beta$ -selenienyl < phenyl <  $\alpha$ -selenienyl <  $\alpha$ -thienyl.



The UV spectra, electric dipole moments, and IR carbonyl-stretching vibrations of the heterocyclic chalcone analogs (6) have been studied.<sup>100</sup> In the electronic spectra, the heterocyclic radicals appear to display a significant electron-donating effect in the excited state (compared with phenyl), giving rise to a bathochromic shift of 31 to 44 m $\mu$ . The heterocycles affect the UV spectrum in the order:  $\alpha$ -selenienyl >  $\alpha$ -thienyl >  $\alpha$ -furyl > phenyl, and the bathochromic

<sup>98</sup> Yu. K. Yur'ev, N. N. Magdesieva, and V. V. Titov, *Zh. Obshch. Khim.* **34**, 1078 (1964); *Chem. Abstr.* **61**, 648 (1964).

<sup>99</sup> Yu. K. Yur'ev, N. N. Magdesieva, and V. V. Titov, *Zh. Obshch. Khim.* **33**, 2158 (1963); *Chem. Abstr.* **59**, 13922 (1963).

<sup>100</sup> S. V. Tsukerman, V. D. Orlov, V. M. Nikitchenko, Yu. S. Rozum, V. F. Lavrushin, and Yu. K. Yur'ev, *Teor. Eksp. Khim.* **2**, 399 (1966); *Chem. Abstr.* **65**, 16839 (1966).

shifts are greater when the heteroatom is represented by X than by Y in (6).<sup>100</sup> The carbonyl vibration frequencies  $\nu_{C=O}$  of compounds (6) usually decrease when phenyl is replaced by a heterocycle; thus IR spectra indicate the electron-donating nature of the heterocyclic rings in the ground state. The furan ring displays the weakest electron-donating effect, and thienyl does not differ significantly from selenienyl.<sup>100</sup>

Dipole moments of the chalcones containing heterocyclic radicals confirm the electron-donor properties of the five-membered heterocycles in their ground states. The moments in these compounds are dominated by the carbonyl polarization which is stronger the more electron-donating is the radical bonded to the carbonyl. Thus, all the physical data on the chalcone analogs suggest that the electron-donating effect of the heteroaromatic radicals decreases in the order:  $\alpha$ -selenienyl >  $\alpha$ -thienyl >  $\alpha$ -furyl.<sup>100</sup>

Spectrophotometry shows that heterocyclic analogs of chalcones<sup>101</sup> when protonated by 100% sulfuric acid dissolved in acetic acid form hydrogen bonds and reveals a positive dynamic conjugation (electromeric) effect which decreases in the series:  $\alpha$ -furyl >  $\alpha$ -selenienyl >  $\alpha$ -thienyl.

The difference in electron influence of five-membered heterocycles which contain O, S, or Se atoms is explained by the fact that the influence is a sum of the positive conjugation and negative induction; thus it operates differently in the static (ground-state mesomeric) or dynamic state. In general, the influence depends on the systems in which it is observed and may be masked by space factors or field effects.

This review shows that the properties and comparative reactivity of five-membered heterocycles containing oxygen, sulfur, and selenium may place selenophene differently with respect to furan and thiophene, and its position in the series depends on the reaction and the role played by the heteroatom. Selenophene is located between furan and thiophene as regards reactions in which the heterocycle displays predominantly electron-donating properties; as for those principally concerned with electron-accepting properties, selenophene is placed between thiophene and benzene.

<sup>101</sup> S. V. Tsukerman, L. A. Kutulya, Yu. N. Surov, V. F. Lavrushin, and Yu. K. Yur'ev, *Dokl. Akad. Nauk SSSR* **164**, 354 (1965); *Chem. Abstr.* **63**, 18006 (1965).

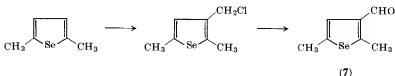


## VI. Reactions of Side-Chain Substituents in the Selenophene Series

This section of the review is concerned with reactions in the side-chain of selenophene derivatives, in which the heterocyclic nucleus exerts an influence, but is not directly attacked.

### A. CHLOROMETHYL SELENOPHENES

The chlorine atom of chloromethyl derivatives of selenophene is very reactive and easily displaced in substitution reactions. Thus, 2-chloromethylselenophene and its homologs readily exchange the chlorine for dialkylamino, alkoxy, and acetoxy groups, and the chloromethyl can be converted into an aldehyde group, providing a synthesis for 2,5-dimethylselenophene-3-aldehyde (7) which cannot be obtained by direct formylation.<sup>102</sup>



Selenophene chloromethyl derivatives readily form di( $\beta$ -hydroxyethyl)aminomethylselenophenes (8) which, with thionyl chloride, give the corresponding di( $\beta$ -chloroethyl)aminomethylselenophenes (9).<sup>103</sup> Chloromethylselenophenes condense with trisubstituted ethylenediamines to yield tetrasubstituted diamines containing the selenophene nucleus.<sup>104</sup> The reaction of 2-chloromethylselenophene with sodium derivatives of malonic and acetoacetic ester yields the acid (10) and ketone (11), respectively, whereas with alkyl magnesium halides 2-(alkylmethyl)selenophenes are formed.<sup>105</sup>

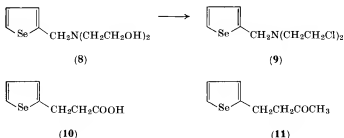
<sup>102</sup> Yu. K. Yur'ev, M. A. Gal'bershtam, and N. K. Sadovaya, *Zh. Obshch. Khim.* **32**, 1301 (1962); *Chem. Abstr.* **58**, 3380 (1963).

<sup>103</sup> Yu. K. Yur'ev, M. A. Gal'bershtam, and G. G. Rozantsev, *Zh. Obshch. Khim.* **32**, 3562 (1962); *Chem. Abstr.* **58**, 13908 (1963).

<sup>104</sup> Yu. K. Yur'ev and M. A. Gal'bershtam, *Zh. Obshch. Khim.* **32**, 3922 (1962); *Chem. Abstr.* **58**, 13909 (1963).

<sup>105</sup> Yu. K. Yur'ev and M. A. Gal'bershtam, *Zh. Obshch. Khim.* **32**, 3249 (1962); *Chem. Abstr.* **58**, 12500 (1963).

2-Chloromethylselenophene and potassium cyanide<sup>106</sup> give selenien-2-ylacetoneitrile; the reaction is not accompanied by rearrangement, unlike that of 2-chloromethylfuran, which with potassium cyanide in protic solvents forms<sup>107</sup> both fur-2-ylacetoneitrile and 2-cyano-5-methylfuran, the latter by  $S_N2'$  displacement and proton shift. 2-Chloromethylthiophene also gives only the normal product; thus furan, alone of the three heterocyclic rings, shows evidence of reduced aromaticity in this reaction.



Thus, halomethyl selenophenes are highly reactive and in their properties closely resemble the corresponding thiophenes.

## B. SELENOPHENE ALDEHYDES AND DERIVED COMPOUNDS

Aldehydes of the selenophene series are typical aromatic aldehydes, as exemplified by the characteristic reactions summarized below.

Selenophene-2-aldehyde takes part in the Hantzsch synthesis [Eq. (1)]<sup>108</sup> and reacts readily with ammonia, aromatic amines and diamines,<sup>109</sup> hippuric, barbituric, and malonic acids, malononitrile,<sup>70</sup> and rhodanine.<sup>109</sup>  $\beta$ -(Selenien-2-yl)acrylic acid has been obtained from selenophene-2-aldehyde by the Perkin reaction and by Knoevenagel condensation with malonic acid.<sup>70</sup> Esters of  $\beta$ -(selenien-2-yl)acrylic acid are easily formed by condensation of the aldehyde

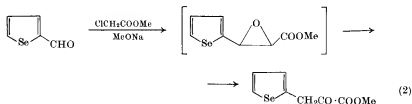
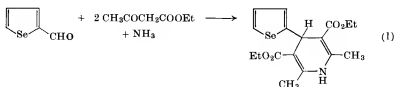
<sup>106</sup> Yu. K. Yur'ev and M. A. Gal'bershtam, *Zh. Obshch. Khim.* **33**, 462 (1963); *Chem. Abstr.* **59**, 1574 (1963).

<sup>107</sup> Yu. K. Yur'ev, N. N. Mezentsova, and T. A. Balashova, *Zh. Obshch. Khim.* **27**, 2536 (1957); *Chem. Abstr.* **52**, 7269 (1958).

<sup>108</sup> K. Yu. Novitskii, Kh. Gresl, and Yu. K. Yur'ev, *Khim. Geterotsikl. Soedin.* **829**, 832 (1966); *Chem. Abstr.* **67**, 32530 (1967).

<sup>109</sup> Yu. K. Yur'ev and N. N. Mezentsova, *Zh. Obshch. Khim.* **28**, 3041 (1958); *Chem. Abstr.* **53**, 9183 (1959).

with alkyl acetates in the presence of sodium.<sup>110</sup> Selenophene-2-aldehyde reacts easily with various methyl ketones under the influence of alkalis, with formation of the corresponding vinyl and divinyl ketones.<sup>71</sup> Condensation of selenophene-2-aldehyde with nitromethane followed by reduction of the resulting  $\alpha, \beta$ -unsaturated nitro compound is a convenient method of synthesizing  $\beta$ -(selenien-2-yl)-ethylamine.<sup>110</sup>  $\alpha$ -Keto esters are formed when selenophene-2-aldehyde reacts with esters of monochloroacetic acid under Darzens conditions [Eq. (2)].<sup>110</sup> Substituted 5-halo-<sup>72</sup> and 5-nitroselenophene-2-aldehydes<sup>47</sup> enter into similar reactions and so a wide variety of compounds containing the haloselenienyl and nitroselenienyl groups can be prepared.



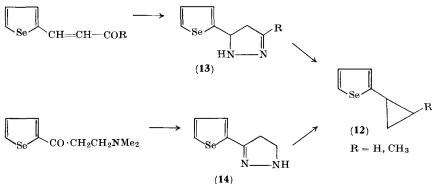
2-Vinylselenophene was obtained from selenophene-2-aldehyde in three ways: decarboxylation of  $\beta$ -(selenien-2-yl)acrylic acid,<sup>111</sup> the Wittig reaction,<sup>112</sup> and dehydration of 1-(selenien-2-yl)ethanol.<sup>111</sup> The most convenient method is the last, conducted in the vapor phase. 2-Vinylselenophene is brominated<sup>112</sup> and formylated in the side chain,<sup>111</sup> and it reacts with diazomethane and *p*-nitrophenyl-diazonium chloride.<sup>112</sup> 2-Cyclopropylselenophene (**12**, R=H) was

<sup>110</sup> Yu. K. Yur'ev, N. N. Mezentsova, and V. E. Vas'kovskii, *Zh. Obshch. Khim.* **29**, 3239 (1959); *Chem. Abstr.* **54**, 13097 (1960).

<sup>111</sup> Yu. K. Yur'ev, N. N. Mezentsova, and V. E. Vas'kovskii, *Zh. Obshch. Khim.* **28**, 3262 (1958); *Chem. Abstr.* **53**, 14086 (1959).

<sup>112</sup> Yu. K. Yur'ev, N. N. Mezentsova, and B. I. Keda, *Zh. Obshch. Khim.* **32**, 1820 (1962); *Chem. Abstr.* **58**, 6817 (1963).

synthesized by Kishner decomposition of the isomeric pyrazolines (13, R = H; and 14) obtained from the action of hydrazine on either  $\beta$ -(selenien-2-yl)acrolein or  $\beta$ -dimethylaminopropionylselenophene hydrochloride; the latter technique is the more convenient. Unlike the above monosubstituted pyrazolines, the disubstituted pyrazoline (13, R = Me) obtained by condensing selenenalacetone with hydrazine hydrate, is quite stable and its decomposition by Kishner's technique yields 2-(2-methylcyclopropyl)selenophene.<sup>113</sup>



Thus, aldehydes of the selenophene series have much in common with other aromatic aldehydes, especially those of the thiophene series.

### C. OTHER ACYL SELENOPHENES

Many reactions of the acyl group of ketones of the selenophene series have been studied. Acyl selenophenes have been shown to be brominated, oxidized, and cyanoethylated, and to undergo the Kishner reduction, Mannich reactions, and Claisen condensations.

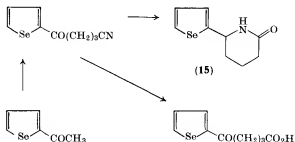
Thus, 5-nitro-2-acetylselenophene is readily brominated by dioxane dibromide, while introduction of bromine into the 4-nitro isomer requires the more drastic conditions of bromine in glacial acetic acid.<sup>114</sup>

Cyanoethylation of acyl selenophenes leads to the formation of  $\delta$ -ketonitriles which are easily converted by alkaline hydrolysis into

<sup>113</sup> Yu. K. Yur'ev, N. N. Mezentsova, and V. E. Vas'kovskii, *Zh. Obshch. Khim.* **30**, 1628 (1960); *Chem. Abstr.* **55**, 1583 (1961).

<sup>114</sup> Yu. K. Yur'ev, E. L. Zaitseva, and A. N. Nikiforova, *Zh. Obshch. Khim.* **30**, 2209 (1960); *Chem. Abstr.* **55**, 10416 (1961).

the respective  $\delta$ -keto acids and, when reduced by formic acid, into substituted piperidones (15).<sup>67</sup>



Ketones of the selenophene series are aminomethylated to give aminoketone hydrochlorides, which with phenylhydrazine form *N*-phenylpyrazolines.<sup>115</sup> Kishner reduction of acyl selenophenes has led to various 2-alkylselenophenes; the Clemmensen technique proved inapplicable for this purpose.<sup>116</sup>

Ketones of the selenophene series can also be used to synthesize  $\alpha$ - and  $\beta$ -dicarbonyl compounds containing the selenienyl group.

The simplest  $\alpha$ -dicarbonyl compound of the selenophene series is obtained by oxidation of 2-acetylselenophene by selenium dioxide.<sup>117</sup> Selenien-2-ylglyoxal is bright yellow and has a high exaltation of molecular refraction (1.87) which is due to conjugation of the two carbonyl groups with the selenophene ring. On standing in air it forms a hemihydrate (colorless crystals). The UV spectrum of (selenien-2-ylglyoxal has two pronounced absorption maxima ( $\lambda_{\max}$  275 and 310  $m\mu$ ); in the spectrum of the hydrate the second maximum disappears.

Methyl selenien-2-yl glyoxal,<sup>118</sup> the simplest  $\alpha$ -diketone of the selenophene series, has been obtained in two ways: by oxidation of 2-propionylselenophene by selenium dioxide and by hydrolysis of the product resulting from nitrosation of that ketone. Its UV spectrum has three characteristic maxima ( $\lambda_{\max}$  277, 283, and 310  $m\mu$ ). When

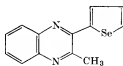
<sup>115</sup> Yu. K. Yur'ev and N. K. Sadovaya, *Zh. Obshch. Khim.* **27**, 1587 (1957); *Chem. Abstr.* **52**, 3780 (1958).

<sup>116</sup> Yu. K. Yur'ev and N. K. Sadovaya, *Zh. Obshch. Khim.* **31**, 3535 (1961); *Chem. Abstr.* **57**, 4620 (1962).

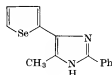
<sup>117</sup> Yu. K. Yur'ev, N. N. Mezentsova, and E. A. Kashutina, *Zh. Obshch. Khim.* **29**, 2597 (1959); *Chem. Abstr.* **54**, 10994 (1960).

<sup>118</sup> Yu. K. Yur'ev, N. N. Magdesieva, and A. T. Monakhova, *Zh. Obshch. Khim.* **35**, 68 (1965); *Chem. Abstr.* **62**, 13114 (1965).

it is treated with 15% aqueous alkali at 0°C there is a benzylic-type rearrangement with formation of  $\alpha$ -(selenien-2-yl)- $\alpha$ -hydroxypropionic acid. The  $\alpha$ -diketone with *o*-phenylenediamine forms a disubstituted quinoxaline (16), and with ammonia and benzaldehyde gives an imidazole (17).



(16)



(17)

The wide application of acetyl selenophenes for the synthesis of  $\beta$ -diketones of the selenophene series containing aliphatic, aromatic, and heterocyclic groups along with the selenienyl, is of considerable interest. Most are easily obtained by the general Claisen technique, the condensation of 2- or 3-acetylselenophene with aliphatic, aromatic, and heterocyclic esters in the presence of sodium amide.<sup>119-121</sup> Bis- $\beta$ -diketones are formed from 2-acetylselenophene and esters of dicarboxylic acids (terephthalic and pyridine-2,6-dicarboxylic acid).<sup>122</sup> The reaction does not lead to  $\beta$ -diketones with a nitro- or hydroxy-group, however, and 2-(*p*-nitrobenzoylacetyl)selenophene is obtained by acylation of the selenenoylacetone-copper complex by *p*-nitrobenzoyl chloride, followed by hydrolysis of the triketone formed.<sup>123</sup>  $\beta$ -Diketones with a nitro group in the selenophene ring have been obtained similarly by acylation of copper complexes of acylacetones with 5-nitro-2-selenenoyl chloride.<sup>124</sup> A  $\beta$ -diketone with a hydroxy group in the benzene ring, 2-(*o*-hydroxybenzoyl-acetyl)selenophene

<sup>119</sup> Yu. K. Yur'ev and N. N. Mezentsova, *Zh. Obshch. Khim.* **31**, 1449 (1961); *Chem. Abstr.* **55**, 23491 (1961).

<sup>120</sup> Yu. K. Yur'ev, N. N. Magdesieva, and V. V. Titov, *Zh. Obshch. Khim.* **32**, 3252 (1962); *Chem. Abstr.* **58**, 12500 (1963).

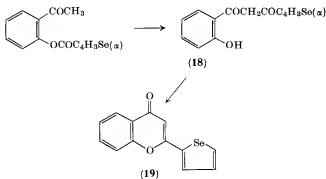
<sup>121</sup> Yu. K. Yur'ev, N. N. Magdesieva, and A. T. Monakhova, *Zh. Org. Khim.* **1**, 1094 (1965); *Chem. Abstr.* **63**, 11474 (1965).

<sup>122</sup> Yu. K. Yur'ev, N. N. Magdesieva, and V. V. Titov, *Zh. Obshch. Khim.* **33**, 1156 (1963); *Chem. Abstr.* **59**, 12744 (1963).

<sup>123</sup> Yu. K. Yur'ev, N. N. Magdesieva, and V. V. Titov, *Zh. Obshch. Khim.* **33**, 2577 (1963); *Chem. Abstr.* **59**, 15248 (1963).

<sup>124</sup> Yu. K. Yur'ev, N. N. Magdesieva, and T. Lesyak, *Khim. Geterotsikl. Soedin.* 902 (1966); *Chem. Abstr.* **66**, 115405 (1967).

(18),<sup>125</sup> has been obtained by the Baker-Venkataraman rearrangement of the *o*-acetophenyl ester of selenophene-2-carboxylic acid by the action of alkali in pyridine. This diketone, however, is unstable and turns easily into 2-(selenien-2-yl)chromone (19).



A detailed study of the acid-base properties of  $\beta$ -diketones of the selenophene series made it possible to evaluate their utility in complex formation and to establish how the dissociation constant of a  $\beta$ -diketone varies with its structure.<sup>126-128</sup>

The structure of  $\beta$ -diketones of the selenophene series was found by physical<sup>129</sup> (UV, IR, and NMR spectra) and chemical<sup>75, 98, 99</sup> (reaction with hydroxylamine) methods.

$\beta$ -Diketones which contain aliphatic, aromatic, or heterocyclic radicals as well as a selenienyl radical have in the UV spectrum two characteristic absorption maxima (280 and 300  $\text{m}\mu$ ) and high absorption intensity almost equal to that of their copper complexes. In the

<sup>125</sup> Yu. K. Yur'ev, N. N. Magdesieva, and V. V. Titov, *Zh. Org. Khim.* **1**, 163 (1965); *Chem. Abstr.* **62**, 14666 (1965).

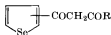
<sup>126</sup> I. P. Efimov, O. D. Lagunova, N. N. Magdesieva, V. V. Titov, Yu. K. Yur'ev, and V. M. Peshkova, *Vestn. Mosk. Univ., Ser. II: Khim.* **18**, No. 5, 49 (1963); *Chem. Abstr.* **60**, 1564 (1964).

<sup>127</sup> A. P. Zozulya, N. N. Mezentsova, V. M. Peshkova, and Yu. K. Yur'ev, *Zh. Anal. Khim.* **14**, 17 (1959); *Chem. Abstr.* **53**, 9760 (1959).

<sup>128</sup> I. P. Efimov, V. V. Titov, N. N. Magdesieva, A. T. Monakhova, Yu. K. Yur'ev, and V. M. Peshkova, *Vestn. Mosk. Univ., Ser. II: Khim.* **21**, No. 2, 90 (1966); *Chem. Abstr.* **65**, 11403 (1966).

<sup>129</sup> N. N. Magdesieva, V. V. Titov, V. F. Bystrov, V. P. Lezina, and Yu. K. Yur'ev, *Zh. Strukt. Khim.* **6**, 402 (1965); *Chem. Abstr.* **63**, 8161 (1965).

IR spectra there is absorption in the region  $1540\text{--}1620\text{ cm}^{-1}$ , characteristic of the chelated *cis*-enol; bands characteristic of a free carbonyl group are absent. The effect of substituents on the enolization of  $\beta$ -diketones (in acetone) was studied by NMR spectroscopy. In the  $\omega$ -acyl-2-acetoselenophene (**20**) and  $\omega$ -acyl-3-acetoselenophene (**21**) series, the acyl groups COR increase the enolization in the following order of R: methyl <  $\alpha$ -furyl <  $\alpha$ -thienyl < trifluoromethyl < phenyl <  $\alpha$ -pyridyl. Thus,  $\beta$ -diketones containing aroyl or heteroaroyl radicals together with selenienyl exist completely as the *cis*-enols.<sup>121</sup>



(20) 2-Selenienyl

(21) 3-Selenienyl

All unsymmetrical diketones can exist in two *cis*-enolic forms. A possible insight into the structures is given by the reaction with hydroxylamine. This involves the assumption, however, that the enolic form of the  $\beta$ -diketone reacts at its carbonyl group to form the monooxime which is then cyclized to the isoxazole. The structures of isoxazoles thus obtained were corroborated by their independent synthesis and, for comparison, the synthesis of their isomers. The enolization of  $\beta$ -diketones has also been discussed in Section V, C.

$\beta$ -Diketones of the selenophene series are used to synthesize various heterocyclic systems: isoxazole, pyrazole, and pyrimidine, as well as  $\alpha$ -substituted bis- $\beta$ -diketones. Thus,  $\beta$ -diketones with hydrazine hydrates yielded the corresponding disubstituted pyrazoles.<sup>130, 131</sup> The presence of the selenienyl radical as a substituent substantially reduced the basicity of a pyrazole ring (see Section V, C); the electron-accepting ability of the selenien-2-yl radical is especially great.<sup>121</sup> The reaction of selenophene  $\beta$ -diketones with ureas gives substituted pyrimidines.<sup>125</sup>

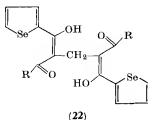
Condensation of  $\beta$ -diketones with formaldehyde in the presence of morpholine or piperidine leads to branched bis- $\beta$ -diketones which exist in the *trans*-enolic form (**22**) as was established by UV and IR

<sup>130</sup> Yu. K. Yur'ev, N. N. Mezentsova, and M. B. Saporovskaya, *Zh. Obshch. Khim.* **32**, 1444 (1962); *Chem. Abstr.* **58**, 6817 (1963).

<sup>131</sup> Yu. K. Yur'ev, N. N. Magdesieva, V. V. Titov, and V. P. Brysova, *Zh. Obshch. Khim.* **33**, 3517 (1963); *Chem. Abstr.* **60**, 8014 (1964).



spectra. Under drastic conditions the *trans-cis* enol isomerization can take place.<sup>122</sup>



## VII. Selenophenes of Practical Importance

### A. SILICONE OXIDATION INHIBITORS

Compounds of the selenophene series are effective high-temperature antioxidants for silicone liquids.<sup>132</sup>  $\beta$ -Diketones, bis- $\beta$ -diketones, and azomethines of the selenophene series have been studied as stabilizers

TABLE V  
RELATIVE EFFECTIVENESS OF INHIBITORS TO THE OXIDATION  
OF PMS AT 300°C

Inhibitors <sup>a</sup>	Gelation time (hr)
Without additives	4
2-Acetoacetylselenophene	11
$\omega$ -Benzoyl-2-acetoselenophene	22
$\omega$ -Picolinoyl-2-acetoselenophene	70
$\omega$ -Nicotinoyl-2-acetoselenophene	56
$\omega$ -Isonicotinoyl-2-acetoselenophene	43
Dipicolinoylbis-2-acetoselenophene	113
N-Salicylal(selenien-2-yl)amine	48
N,N'-Di(selenen-2-yl)ethylenediamine	60
N,N'-Di(selenen-2-yl)hexamethylenediamine	62
Dibenzoylmethane	9
Thenoyl-2-benzoylmethane	12
Dilaurylselenide	20

<sup>a</sup> Inhibitor 0.5% w/w.

<sup>132</sup> R. I. Kobzova, E. M. Oparina, N. K. Levkina, N. N. Magdesieva, and Yu. K. Yur'ev, *Zh. Prikl. Khim.* **39**, 1638 (1966); *Chem. Abstr.* **65**, 15509 (1966).

for various silicone liquids: polymethyl-siloxane PMS-100, polymethyl phenylsiloxane with low content of phenyl substituents, PM-1322/300, and polymethyl-chlorophenylsiloxane (PMCPs). Their stability toward thermal oxidation was measured by the time required for the liquids to gel when heated to a certain temperature with or without various additives (0.5% w/w) (see Table V). Selenophenes are more effective inhibitors than dilaurylselenide. Of the selenophene  $\beta$ -diketones studied, those containing the  $\beta$ -,  $\gamma$ -, and especially the  $\alpha$ -pyridyl radicals were most effective. The bis- $\beta$ -diketone, dipicolinoylbis-2-acetoselenophene is still more effective and increases the stability of PMS-100 twenty-eight times. The  $\beta$ -diketones which contain no selenieryl radical, such as dibenzoylmethane and thenoyl-2-benzoylmethane, were found to be less effective inhibitors under these conditions, which indicates the significance of a cyclically bonded selenium atom in the antioxidant molecule.

Selenieryl azomethines are also highly active as oxidation inhibitors.

For stabilization of PCMPS, 2-acetoacetylselenophene is very effective at 0.5% w/w.

## B. COMPLEXING AGENTS

Selenophene  $\beta$ -diketones can be used as extractants for the separation and isolation of metals. The advantages of selenophene  $\beta$ -diketones were revealed by comparison of their dissociation and distribution constants with those of acetylacetone, benzoylacetone, thenoyl-trifluoromethylacetone, etc. Selenophene  $\beta$ -diketones containing a trifluoromethyl group and a pyridyl radical were of particular interest. 2-Acetoacetylselenophene<sup>127</sup> is better for the extraction of thorium from water than acetylacetone, previously extensively used.

To separate zirconium from hafnium, 2-thenoyltrifluoroacetone is less effective than the selenophene analog, which yields hafnium solutions of 98–99% purity; thus, the two similar elements can be efficiently separated.<sup>133</sup>

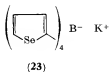
Selenophene  $\beta$ -diketones containing  $\alpha$ -,  $\beta$ -, or  $\gamma$ -pyridyl radicals can be used for extraction of neodymium; the extraction percentage is approximately 90%. The most practical is  $\omega$ -picolinoyl-2-aceto-selenophene which gives a high percentage of metal extraction at a

<sup>133</sup> N. V. Mel'chakova, N. N. Magdesieva, Yu. K. Yur'ev, and V. M. Peshkova, *Vestn. Mosk. Univ., Ser. II: Khim.* **21**, No. 4, 82 (1966); *Chem. Abstr.* **66**, 14495 (1967).

lower pH value<sup>134</sup> than 8-hydroxyquinoline which has been widely used in analytical chemistry.<sup>135</sup>

The luminescence of various chelated compounds of the rare earths is very promising because their spectral and luminescent properties help to solve a number of theoretical and applied problems. Luminescence spectra of europium complexes with selenophene  $\beta$ -diketones have been studied as a function of the ligand structure. Of the spectra obtained,  $\omega$ -picolinoyl-2-acetoselenophene and diselenoylmethane look most promising for obtaining induced radiation.<sup>136</sup>

Of various rare earth 2-selenenoylacetone chelates luminescence was found only in the europium compounds. Physicochemical properties and IR spectra of 2-selenenoylacetates of rare earths (except cerium and promethium) give information regarding the structure of these complexes as a function of the metal.



Other compounds of the selenophene series such as potassium tetra( $\alpha$ -selenienyl)borate (23), obtained by interaction of  $\alpha$ -selenienylmagnesium iodide with potassium tetrafluoroborate, precipitate rubidium ions and, more completely, cesium and quaternary ammonium ions from water solutions and can be used as analytical reactants for those ions.<sup>81</sup>

### C. BIOLOGICALLY ACTIVE COMPOUNDS

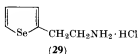
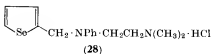
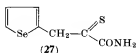
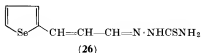
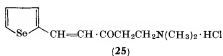
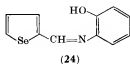
The physiological activity of compounds of the selenophene series ensures their practical importance. Many selenophene aldehydes act bacteriostatically *in vitro* on acid-resistant bacteria and fungistatically

<sup>134</sup> V. M. Peshkova, I. P. Efimov, and N. N. Magdesieva, *Zh. Anal. Khim.* **21**, 499 (1966); *Chem. Abstr.* **65**, 4986 (1966).

<sup>135</sup> G. H. Morrison and H. Freiser, "Solvent Extraction in Analytical Chemistry." Wiley, New York, 1957.

<sup>136</sup> O. L. Lebedev, N. N. Magdesieva, A. V. Michurina, Kh. A. Ainitdinov, and Yu. K. Yur'ev, *Zh. Strukt. Khim.* **7**, 522 (1966); *Chem. Abstr.* **66**, 6842 (1967).

on parasitic fungi. The most active were found<sup>21</sup> to be compounds 24-27.



Some selenophenes have a pronounced antihistamine activity, e.g., 28.<sup>137</sup> Monoamines containing a selenienyl radical, e.g., the  $\beta$ -ethylamine (29)<sup>21</sup> have psychotropic properties and should be further studied because they might be used in medical practice as anti-depressants.

<sup>137</sup> A. N. Kudrin, L. F. Chernyshova, M. A. Gal'bershtam, and Yu. K. Yur'ev, *Farmakol. i Toksikol.* **6**, 692 (1964); *Chem. Abstr.* **62**, 13703 (1965).

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# 3-Piperideines (1,2,3,6-Tetrahydropyridines)

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## I. Introduction

The three possible tetrahydropyridines, namely, 2,3,4,5-tetrahydropyridine or 1-piperideine (1), 1,2,3,4-tetrahydropyridine or 2-piperideine (2), and 1,2,3,6-tetrahydropyridine or 3-piperideine (3), are all known in the form of derivatives, but only 3-piperideine (3) has been prepared as a stable free base.



(1)



(2)



(3)

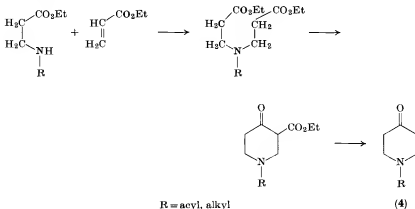
Since there have been many publications in the last few years on the syntheses and reactions of 3-piperideines, it seemed appropriate to compile the present review covering the literature to 1968.

The chemistry of 3-piperideines has also been the subject of some earlier reviews<sup>1</sup> or chapters in monographs.<sup>1a</sup>

## II. Methods of Preparation

### A. MISCELLANEOUS SYNTHETIC METHODS

One of the most frequent routes to 3-piperideines makes use of 4-piperidones (4) as intermediates. The latter compounds are prepared, e.g., by the addition of alkyl 3-acylaminopropionates or 3-alkylaminopropionates to alkyl acrylates and subsequent Dieckmann condensation.

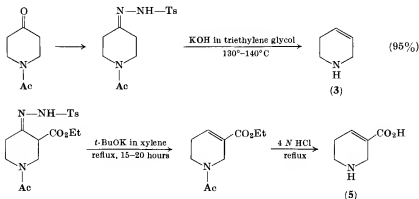


The parent 3-piperideine (3) was prepared from 1-acetyl-4-piperidone by conversion into the *p*-toluenesulfonylhydrazone and thermal fission of the latter in alkaline media (the Bamford-Stevens reac-

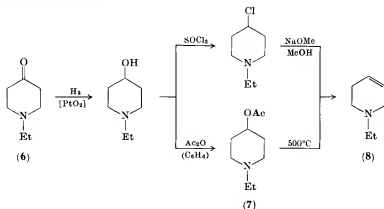
<sup>1</sup> J. J. Panouse, *Bull. Soc. Chim. France* D 60 (1953); Yu. A. Berlin and A. N. Kost, *Usp. Khim.* **29**, 220 (1960).

<sup>1a</sup> M. Ferles and J. Jizba, "Chemistry of Pyridine" (in Czech), p. 532. Publ. House of Czechoslovak Acad. Sci., Prague, 1957; H. S. Mosher, in "Heterocyclic Compounds" (R. R. Elderfield, ed.), Vol. I, pp. 626-631. Wiley, New York, 1950; N. Campbell, in "Chemistry of Carbon Compounds" (E. H. Rodd, ed.), Vol. IV, pp. 567-569. Elsevier, Amsterdam, 1957.

tion).<sup>1b, 2</sup> Guvacine (3-piperideine-3-carboxylic acid, **5**) was obtained similarly.<sup>2</sup>



In the preparation of 1-ethyl-3-piperideine (**8**), the starting material 1-ethyl-4-piperidone (**6**) was hydrogenated to give 1-ethyl-4-piperidinol. Treatment of the latter with thionyl chloride afforded 1-ethyl-4-chloropiperidine, the dehydrohalogenation of which (NaOMe/MeOH) led to a low yield of 1-ethyl-3-piperideine. A somewhat higher yield (37%) was obtained by pyrolysis (500°C) of 1-ethyl-4-acetoxypiperidine (**7**).<sup>3</sup>



<sup>1b</sup> V. Carelli and F. Morlacchi, *Ann. Chim. (Rome)* **54**, 1291 (1964); *Chem. Abstr.* **62**, 11769 (1965).

<sup>2</sup> F. Morlacchi, M. Cardellini, and F. Liberatore, *Ann. Chim. (Rome)* **57**, 1456 (1967); *Chem. Abstr.* **69**, 2817 (1968).

<sup>3</sup> N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.* **76**, 2781 (1954).



1-Phenyl-3-piperidine was obtained<sup>4</sup> similarly via 1-phenyl-4-piperidone and 1-phenyl-4-piperidinol, which was then converted by heating with fuming hydrobromic acid in a sealed tube to 1-phenyl-4-bromopiperidine, and this was dehydrohalogenated in methanolic potassium hydroxide.

1-Alkyl-4-aryl-3-piperideines (9) may be obtained from 1-alkyl-4-piperidones by treatment with arylmagnesium halides and dehydration of the resulting tertiary carbinols (Table I). The dehydration is

TABLE I  
PREPARATION OF 1-ALKYL-4-  
ARYL-3-PIPERIDEINES



R	Ar	Reference
Me	<i>o</i> -Anisyl	5
Me	<i>m</i> -Hydroxyphenyl	5
Me	<i>p</i> -Anisyl	5, 6
Me	Phenyl	5, 7
Me	1-Naphthyl	8
Me	2-Naphthyl	8
Me	2-Pyridyl	8
Me	2-Thienyl	8
Me	3-Thienyl	8
Et	<i>p</i> -Anisyl	5, 6
Bu	Phenyl	5, 7

effected by potassium hydrogen sulfate (160°C/10 mm), or by a refluxing mixture of acetic acid and 48% hydrobromic acid, or by thionyl chloride.

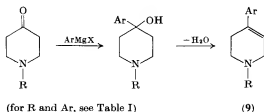
<sup>4</sup> V. Hahn, E. Cerkovnikov, and V. Prelog, *Ber.* **74**, 1658 (1941).

<sup>5</sup> A. Ziering, L. Berger, S. D. Heineman, and J. Lee, *J. Org. Chem.* **12**, 894 (1947).

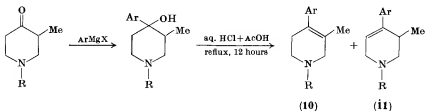
<sup>6</sup> R. H. K. Foster and A. J. Carman, *J. Pharmacol. Exptl. Therap.* **91**, 195 (1947); *Chem. Abstr.* **42**, 983 (1948).

<sup>7</sup> S. M. McElvain and J. C. Safranski, *J. Am. Chem. Soc.* **72**, 3134 (1950).

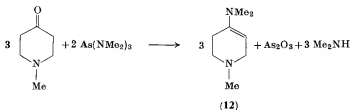
<sup>8</sup> S. Oshiro, *J. Pharm. Soc. Japan* **75**, 658 (1955); *Chem. Abstr.* **50**, 3436 (1956).



Dehydration of 1-alkyl-3-methyl-4-aryl-4-piperidinol in hydrochloric acid and acetic acid afforded a mixture of isomeric piperideines (10), (11).<sup>9, 10</sup>



Treatment of 1-methyl-4-piperidone with tris(dimethylamino)arsine gave an enamine, viz., 1-methyl-4-dimethylamino-3-piperideine (12).<sup>11</sup>



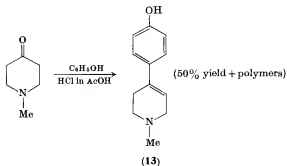
1-Methyl-4-(*p*-hydroxyphenyl)-3-piperideine (13) was prepared by the reaction of 1-methyl-4-piperidone with phenol (2,4-dimethylphenol reacted analogously). It is noteworthy that 3-substituted 4-piperidones do not react with phenol at all.<sup>12</sup>

<sup>9</sup> A. F. Casy, A. H. Beckett, M. A. Iorio, and H. Z. Youssef, *Tetrahedron* **21**, 3387 (1965).

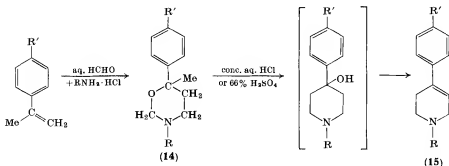
<sup>10</sup> A. F. Casy, A. H. Beckett, and M. A. Iorio, *Tetrahedron* **23**, 1405 (1967).

<sup>11</sup> H. Hirsch, *Ber.* **100**, 1289 (1967).

<sup>12</sup> S. M. McElvain and R. S. Berger, *J. Am. Chem. Soc.* **77**, 2848 (1955).



Some 1-alkyl-4-aryl-3-piperidineins are obtained from  $\alpha$ -methylstyrene and its derivatives by the reaction with formaldehyde and hydrochloride of a primary amine, rearrangement of the resulting oxazine derivative (14) with sulfuric acid or hydrochloric acid to 1-alkyl-4-aryl-4-piperidinol, and dehydration of the latter.<sup>13-15</sup>



R	Me	Et	n-C <sub>6</sub> H <sub>13</sub>	CH <sub>2</sub> :CHCH <sub>2</sub>	PhCH <sub>2</sub>	Me	PhCH <sub>2</sub>
R'	H	H	H	H	H	Me	Me
Yield (%)	86	71	6	23	66	84	42

In some cases, this synthesis may be simplified by omission of isolation at the oxazine stage. Thus, 1-methyl-4-phenyl-3-piperidineine (15; R = Me, R' = H) may be obtained directly in 52% yield by heating

<sup>13</sup> C. J. Schmidle and R. C. Mansfield, *J. Am. Chem. Soc.* **77**, 5698 (1955).

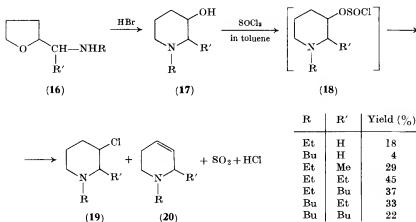
<sup>14</sup> P. A. J. Janssen, Belgian Patent 577,977 (1959); *Chem. Abstr.* **54**, 4629 (1960).

<sup>15</sup> C. J. Schmidle and R. C. Mansfield, *J. Am. Chem. Soc.* **78**, 425 (1956).

a mixture of  $\alpha$ -methylstyrene, aqueous formaldehyde, and methylamine hydrochloride to 75°C, adding sulfuric acid, and heating again (90°–95°C).<sup>15</sup>

With the use of ammonium chloride instead of alkylammonium chlorides, 4-aryl-3-piperideines unsubstituted at position 1 are obtained.<sup>14</sup>

An interesting synthesis of 1,2-dialkyl-3-piperideines (**20**) consists in a ring enlargement of tetrahydrofurfurylamine derivatives (**16**) by the action of hydrogen bromide to 1,2-dialkyl-3-piperidinols (**17**) and treatment of the latter with thionyl chloride in toluene. Some 1,2-dialkyl-3-piperideines (**20**) were contaminated with the corresponding 1,2-dialkyl-3-chloropiperidines (**19**). Because of the mild conditions in the "dehydration" stage, the chlorosulfites (**18**) rather than the 3-chloropiperidines (**19**) are assumed as intermediates.<sup>16</sup>



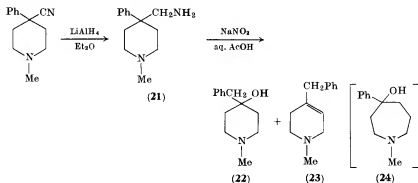
An analogous reaction sequence (except for the use of chloroform as the solvent in the thionyl chloride treatment) was applied in the preparation of 1-ethyl-4-benzyl-3-piperideine.<sup>17</sup>

1-Methyl-4-phenyl-4-cyanopiperidine, an intermediate in the synthesis of a Lerone-like compound (see Section VI), may be reduced to a primary amine (**21**), the treatment of which with nitrous acid results in rearrangement with the formation of a mixture of 1-methyl-4-benzyl-4-piperidinol (**22**) and 1-methyl-4-benzyl-3-piperideine

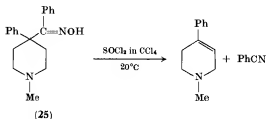
<sup>16</sup> R. Paul and S. Tehelitcheff, *Bull. Soc. Chim. France* **21**, 982 (1954).

<sup>17</sup> R. L. Clarke, U.S. Patent 3,301,865 (1967); *Chem. Abstr.* **67**, 21839 (1967).

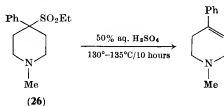
(23).<sup>18</sup> The expected Demjanov ring enlargement of **21** to hexahydro-1-methyl-4-phenyl-4-azepinol (**24**) did not occur.



The oxime of 1-methyl-4-phenyl-4-benzoylpiperidine (**25**) was found to decompose by the action of thionyl chloride with formation of 1-methyl-4-phenyl-3-piperidine and benzonitrile.<sup>19</sup>



1-Methyl-4-phenyl-3-piperidine is also formed from 1-methyl-4-phenyl-4-ethylsulfonylpiperidine (**26**) by heating in 50% aqueous sulfuric acid (along with unexamined sulfur-containing compounds.)<sup>20</sup>

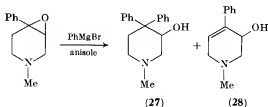


<sup>18</sup> J. Diamond, W. F. Bruce, and F. T. Tyson, *J. Org. Chem.* **30**, 1840 (1965).

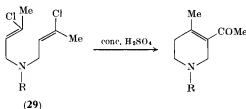
<sup>19</sup> R. E. Lyle and G. G. Lyle, *J. Org. Chem.* **18**, 1058 (1953).

<sup>20</sup> J. Büchi, M. Prost, H. Eichenberger, and R. Lieberherr, *Helv. Chim. Acta* **35**, 1527 (1952).

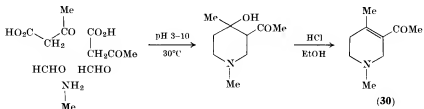
Treatment of 1-methyl-4-phenyl-3,4-epoxypiperidine with phenylmagnesium bromide in refluxing anisole affords a mixture of 1-methyl-4,4-diphenyl-3-piperidinol (27) and 1-methyl-4-phenyl-5-hydroxy-3-piperideine (28).<sup>21</sup>



3-Acetyl-4-methyl-3-piperideine and some *N*-substituted derivatives were prepared from bis(2-chlorocrotyl)amine<sup>22</sup> (29) or its *N*-methyl, *N*-benzyl, *N*-benzoyl, or *N*-*p*-toluenesulfonyl derivatives by the action of concentrated sulfuric acid.<sup>23</sup>



1,4-Dimethyl-3-acetyl-3-piperideine (30) is formed from acetoacetic acid, formaldehyde, and methylamine hydrochloride.<sup>24</sup>



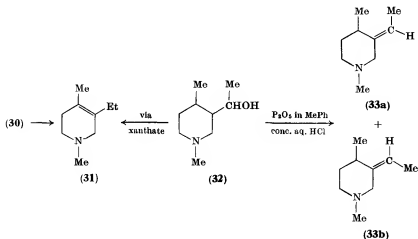
<sup>21</sup> R. E. Lyle and W. E. Krueger, *J. Org. Chem.* **32**, 2873 (1967).

<sup>22</sup> O. Wichterle and M. Hudlický, *Collect. Czech. Chem. Commun.* **12**, 101 (1947).

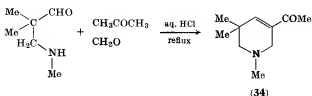
<sup>23</sup> R. Lukeš, M. Hudlický, and Z. Janů, *Collect. Czech. Chem. Commun.* **21**, 140 (1956).

<sup>24</sup> V. Prelog, A. Komzak, and E. Moor, *Helv. Chim. Acta* **25**, 1654 (1942).

The acetyl derivative (30) may be converted by Wolff-Kishner reduction into 1,4-dimethyl-3-ethyl-3-piperidine (31).<sup>25</sup> The latter compound is obtained in 17% yield also by dehydration of 1,4-dimethyl-3-(1-hydroxyethyl)piperidine (32) by the xanthate method.<sup>26</sup> On the other hand, dehydration of the carbinol (32) with phosphorus pentoxide in toluene or by heating in concentrated hydrochloric acid gives a mixture of isomeric 1,4-dimethyl-3-ethylidenepiperidines (33a, b).<sup>26</sup>



Some substituted 3-piperideines are accessible via the Mannich synthesis. Thus, refluxing a mixture of formaldehyde, acetone, and the hydrochloride of the Mannich base previously prepared from formaldehyde, isobutyraldehyde, and methylamine hydrochloride affords 1,5,5-trimethyl-3-acetyl-3-piperideine (34).<sup>27</sup>

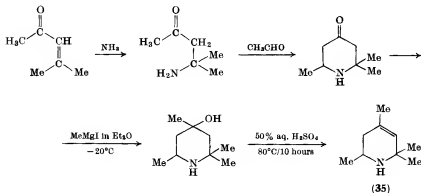


<sup>25</sup> V. Prelog and A. Komzak, *Ber.* **74**, 1705 (1941).

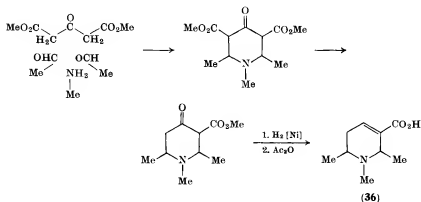
<sup>26</sup> V. Prelog and E. Moor, *Helv. Chim. Acta* **28**, 182 (1945).

<sup>27</sup> C. Mannich and E. Buchholzer, *Ber.* **80**, 19 (1947).

2,2,4,6-Tetramethyl-3-piperideine (35) may be prepared from mesityl oxide via diacetoneamine (4-amino-4-methyl-2-pentanone) and reaction with acetaldehyde to give 2,2,6-trimethyl-4-piperidone, which is then treated with methylmagnesium iodide and dehydrated.<sup>28</sup>



Condensation of dimethyl acetonedicarboxylate with acetaldehyde and methylamine led to dimethyl 1,2,6-trimethyl-4-piperidone-3,5-dicarboxylate, further reactions of which yielded a 2,6-dimethyl analog of arecaine (36)<sup>29, 30</sup> (see also Section V, A.)



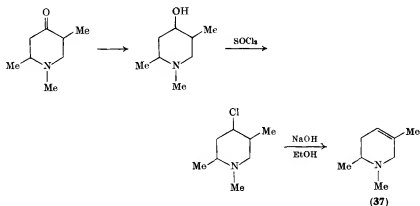
<sup>28</sup> E. Matter, *Helv. Chim. Acta* **31**, 612 (1948).

<sup>29</sup> P. S. Ugryumov, *Dokl. Akad. Nauk SSSR* **29**, 48 (1940); *Chem. Abstr.* **35**, 3644 (1941).

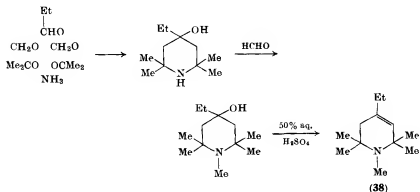
<sup>30</sup> P. S. Ugryumov, *Zh. Obshch. Khim.* **11**, 829 (1941); *Chem. Abstr.* **36**, 4125 (1942).



1,3,6-Trimethyl-3-piperideine (37) may be obtained from 1,2,5-trimethyl-4-piperidone by hydrogenation, conversion of the resulting alcohol into the chloro derivative, and dehydrohalogenation of the latter.<sup>31</sup>



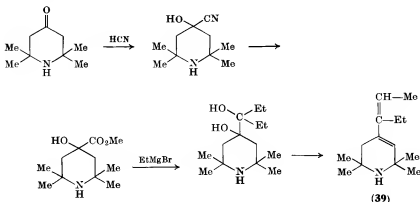
1,2,2,6,6-Pentamethyl-4-ethyl-3-piperideine (38) was claimed as the product from formaldehyde, propionaldehyde, acetone, and ammonia by the following sequence,<sup>32</sup> but this curious reaction needs confirmation.



<sup>31</sup> I. N. Nazarov, N. S. Prostakov, N. N. Mikheeva, and N. A. Fradkina, *Zh. Obshch. Khim.* **29**, 2609 (1959); *Chem. Abstr.* **54**, 11012 (1960).

<sup>32</sup> W. R. Wragg and G. F. Lee, British Patent 849,282 (1960); *Chem. Abstr.* **55**, 8434 (1961).

2,2,6,6-Tetramethyl-4-(1-ethylpropenyl)-3-piperideine (**39**) may be prepared from 2,2,6,6-tetramethyl-4-piperidone (triacetoneamine).<sup>33</sup>



An interesting route leading to 3-piperideines by Merten and Müller<sup>34, 35</sup> consists in a  $\text{BF}_3$ -catalyzed condensation of substituted 1,3-butadienes with methylenebiscarbamates,  $\text{H}_2\text{C}(\text{NHCO}_2\text{R})_2$ , or arylmethylenebiscarbamates,  $\text{ArCH}(\text{NHCO}_2\text{R})_2$ , to give a mixture of the carbamate  $\text{H}_2\text{NCO}_2\text{R}$  and 1-alkoxycarbonyl-3-piperideine ( $\text{Ar} = \text{H}$ ) or 2-aryl-1-alkoxycarbonyl-3-piperideines (**40a**, **b**). This condensation is reminiscent of the Diels-Alder reaction for diene cycloaddition with methylenebiscarbamate in the role of a precursor of the dienophile. Removal of the *N*-alkoxycarbonyl group requires forcing conditions (e.g., aqueous ethanolic potassium hydroxide, 210°–240°C).<sup>34</sup>



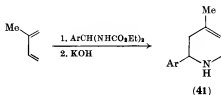
By use of methylenebisdiethylcarbamate, *N*-ethoxycarbonyl-3-piperideines have been prepared from the following dienes: butadiene,

<sup>33</sup> L. Orthner, *Ann.* **459**, 217 (1927).

<sup>34</sup> R. Merten and G. Müller: *Angew. Chem.* **74**, 866 (1962).

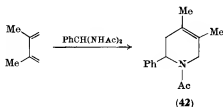
isoprene, chloroprene, 2,3-dimethylbutadiene, 1-phenylbutadiene, and ethyl hexa-2,4-dienoate.<sup>34</sup>

The reaction of isoprene with arylmethylenebisdiethylcarbamates and subsequent removal of the *N*-ethoxycarbonyl group has been reported to give the following 6-substituted 4-methyl-3-piperideines (41) (substituents at position 6 given).<sup>34</sup>



Ar = H, Ph, *p*-MeC<sub>6</sub>H<sub>4</sub>, *o*-ClC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *o*-MeOC<sub>6</sub>H<sub>4</sub>, 3,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>

Instead of methylenebiscarbamates, acylated aldehyde aminsals may be used in some cases. Thus, for example, the reaction of 2,3-dimethyl-1,3-butadiene and benzalbisacetamide has been reported to afford 1-acetyl-3,4-dimethyl-6-phenyl-3-piperideine (42).<sup>34</sup>

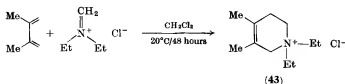


The methylenebiscarbamate reaction of 1,3-dienes was used in the synthesis of the alkaloid anatabine (see Section V, B) and 4-methyl-3-piperideine, an intermediate in the synthesis of the pharmaceutical Lerone (see Section VI).

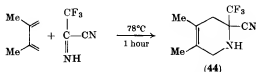
1,1-Diethyl-3,4-dimethyl-3-piperideinium chloride (43) may be prepared by the Diels-Alder reaction of 2,3-dimethyl-1,3-butadiene and diethylchloromethylamine ClCH<sub>2</sub>NEt<sub>2</sub>. The latter compound reacts in the form of methylenediethylimmonium chloride (CH<sub>2</sub>:N<sup>+</sup>Et<sub>2</sub>)Cl<sup>-</sup>.<sup>36</sup>

<sup>35</sup> R. Merten, Belgian Patent 608,904 (1962); *Chem. Abstr.* **59**, 2781 (1963).

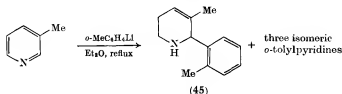
<sup>36</sup> H. Böhme, K. Hartke, and A. Müller; *Ber.* **96**, 607 (1963).



The Diels-Alder reaction of 2,3-dimethyl-1,3-butadiene and  $\alpha$ -iminotrifluoropropionitrile gives 3,4-dimethyl-6-cyano-6-trifluoromethyl-3-piperideine (44) in 80% yield.<sup>37</sup>



Nonreductive syntheses of 3-piperideines from pyridine derivatives are not numerous. For example, treatment of 3-methylpyridine with *o*-tolyllithium was reported to give a mixture of 2-*o*-tolyl-3-methyl-3-piperideine (45) and three isomeric methyl *o*-tolylpyridines, formed by disproportionation of the dihydro intermediates.<sup>38</sup>



The Freund reaction of 3,4-dimethylpyridine methobromide and benzylmagnesium bromide affords a mixture of two isomeric dihydropyridines (46a, b). The partial reduction of the latter isomer to 1,3,4-trimethyl-6-benzyl-3-piperideine (47) was performed by hydrogenation (Pd/BaSO<sub>4</sub>), or by the action of sodium borohydride, or on treatment of the perchlorate with lithium aluminum hydride.<sup>39</sup>

1,2-Dimethyl-3-piperideine<sup>40</sup> (48) and 1-phenethyl-2-*p*-methoxybenzyl-3,4-dimethyl-3-piperideine<sup>41</sup> (49) were prepared analogously

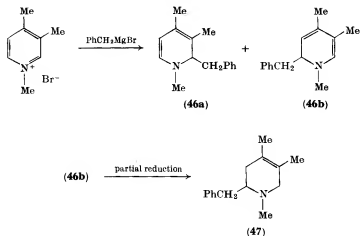
<sup>37</sup> W. J. Middleton and C. G. Krespan, *J. Org. Chem.* **33**, 3625 (1968).

<sup>38</sup> R. A. Abramovitch and G. A. Poulton, *Chem. Commun.*, 274 (1967).

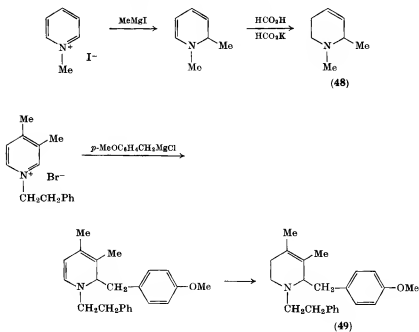
<sup>39</sup> E. L. May and E. M. Fry, *J. Org. Chem.* **22**, 1366 (1957); E. M. Fry, *ibid.* **28**, 1869 (1963).

<sup>40</sup> R. Lukeš and V. Dienstbierová, unpublished results.

<sup>41</sup> D. E. Rivard, U.S. Patent 3,073,837 (1963); *Chem. Abstr.* **58**, 12521 (1963).



to compound **47**, i.e., by a combination of the Freund reaction and partial reduction. In the case of compound **48**, the partial reduction was performed by formate-formic acid mixture.

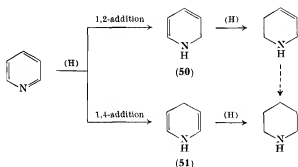


## B. REDUCTION OF PYRIDINE DERIVATIVES

3-Piperideines unsubstituted at the nitrogen atom may be prepared from the corresponding pyridine compounds by partial reduction with sodium and boiling alcohols (the Ladenburg reduction), by electrolytic reduction, or, preferably, by reduction with aluminum hydride. 1-Alkyl-3-piperideines are prepared by reduction of quaternary pyridinium salts with formic acid (the Lukeš reduction) or with complex hydrides.

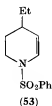
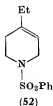
1. *The Ladenburg Reduction*

Reduction of pyridine bases with sodium and alcohols usually affords the corresponding piperidines. In some cases, however, especially with the 4-substituted pyridines, the resulting hexahydro bases are accompanied by a lesser amount of the tetrahydro compounds, i.e., 3-piperideines. The first molecule of hydrogen can add in the 1,2- or 1,4- position to the pyridine ring with formation of **50** and **51**, respectively. Both double bonds of the 1,4-dihydro derivative (**51**) are capable of further reduction to give the piperidine. In the 1,2-dihydro derivative (**50**), however, only the  $\alpha,\beta$  double bond is reduced further. When position 4 is occupied by a substituent, the 1,2-addition leading to 3-piperideines is preferred. It is noteworthy that 3-piperideines are resistant to reduction with sodium in boiling alcohols, but may be converted into the hexahydro bases by catalytic hydrogenation.



In the early investigations on the Ladenburg reduction there were some observations of the formation of tetrahydro derivatives, but the

position of the remaining double bond was not determined.<sup>42-44</sup> According to Wawzonek *et al.*, the proportion of the tetrahydro derivatives of some pyridine homologs increases when the reduction is performed in butanol (instead of in ethanol) and the sodium is added very rapidly.<sup>45</sup> One product was suggested to be 4-ethyl-3-piperidine on the basis of the stability of the corresponding *N*-benzenesulfonyl derivative (52) toward alkali [in the case of the isomeric 1-benzenesulfonyl-4-ethyl-2-piperidine (53) ring opening may be expected, with formation of an aminoaldehyde].<sup>45</sup>



The tetrahydro derivatives are usually separated from the hexahydro bases by addition of bromine to the remaining double bond. The mixture of bases is dissolved in hydrobromic acid and a solution of bromine in hydrobromic acid is added until the red color of bromine persists. The mixture is reduced in volume, and the crystals of 3-piperidine dibromide hydrobromide are filtered off and purified by crystallization. The more soluble hydrobromides of the hexahydro bases remain in the mother liquors. The unsaturated base is recovered from the dibromide hydrobromide by treatment in aqueous solution with zinc dust.<sup>43</sup> More recently, preparative gas chromatography was successfully used to obtain a pure tetrahydro base free of isomers and the related hexahydro compounds.<sup>46</sup>

The Ladenburg reduction of 3-methylpyridine,<sup>47</sup> 4-methylpyridine,<sup>47</sup> 4-ethylpyridine,<sup>48</sup> and 2-methyl-5-ethylpyridine<sup>48</sup> was

<sup>42</sup> A. E. Tschitschibabin, *Zh. Russ. Fiz. Khim. Obshchest.* **34**, 508 (1902).

<sup>43</sup> W. Koenigs and K. Bernhart, *Ber.* **38**, 3042, 3049, 3928 (1905).

<sup>44</sup> W. Koenigs, *Ber.* **40**, 3199 (1907).

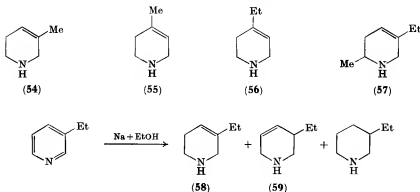
<sup>45</sup> S. Wawzonek, M. F. Nelson, and P. J. Thelen, *J. Am. Chem. Soc.* **74**, 2894 (1952).

<sup>46</sup> J. Janák, M. Holík, and M. Ferles, *Collect. Czech. Chem. Commun.* **31**, 1273 (1966); M. Holík, J. Janák, and M. Ferles, *ibid.* **32**, 3546 (1967).

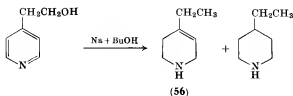
<sup>47</sup> M. Ferles, *Collect. Czech. Chem. Commun.* **24**, 1029 (1959).

<sup>48</sup> M. Ferles, M. Havel, and A. Tesařová, *Collect. Czech. Chem. Commun.* **31**, 4121 (1966).

found to give mixtures of the corresponding hexahydro compounds and a substituted 3-piperideine, the alkyl group of which was attached to the double bond, namely, 3-methyl-3-piperideine<sup>47</sup> (54), 4-methyl-3-piperideine<sup>47</sup> (55), 4-ethyl-3-piperideine<sup>48</sup> (56), and 3-ethyl-6-methyl-3-piperideine<sup>48</sup> (57). On the other hand, reduction of 3-ethylpyridine<sup>48</sup> gave the hexahydro base and isomeric tetrahydro bases, viz., 3-ethyl-3-piperideine (58) and 5-ethyl-3-piperideine (59).



4-Ethyl-3-piperideine (56) is also formed as a by-product in the reduction of 4- $\beta$ -hydroxyethylpyridine with sodium in boiling butanol.<sup>49</sup>



The Ladenburg reduction of 4-*sec*-butylpyridine gives a mixture of a saturated and an unsaturated base, the latter probably being 4-*sec*-butyl-3-piperideine.<sup>50</sup>

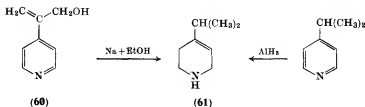
Reduction of 2-(4-pyridyl)propenol (60)<sup>51</sup> with sodium in ethanol and the aluminum hydride reduction of 4-isopropylpyridine<sup>48</sup> afford the same product, 4-isopropyl-3-piperideine (61).

<sup>49</sup> R. Lukeš and M. Ferles, *Collect. Czech. Chem. Commun.* **20**, 1227 (1955).

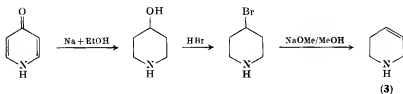
<sup>50</sup> R. Lukeš and I. Ernest, *Collect. Czech. Chem. Commun.* **15**, 107 (1950).

<sup>51</sup> R. Lukeš and J. Plešek, *Collect. Czech. Chem. Commun.* **21**, 1305 (1956).

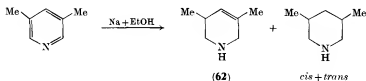




The parent 3-piperidine (3) was first prepared (in the form of its hydrochloride) by Ladenburg reduction of 4-pyridone, conversion of the resulting 4-piperidinol into 4-bromopiperidine, and dehydrohalogenation of the latter.<sup>52</sup>



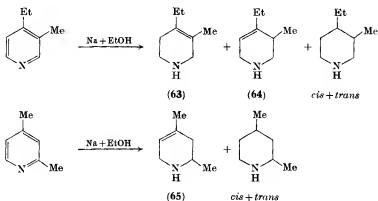
In addition to 2-methyl-5-ethylpyridine mentioned above, the following dialkylpyridines have been reduced by the Ladenburg method: 3,5-dimethylpyridine,<sup>53</sup> 3-methyl-4-ethylpyridine,<sup>48</sup> and 2,4-dimethylpyridine.<sup>48</sup> 3,5-Dimethyl-3-piperidine (62) and *cis*- and *trans*-3,5-dimethylpiperidine are obtained from 3,5-dimethylpyridine.<sup>53</sup>



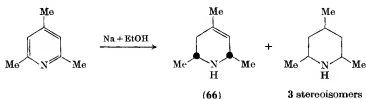
Two 3-piperidine (63 and 64) and two piperidines (*cis* and *trans* isomers) are obtained by the Ladenburg reduction of 4-ethyl-3-methylpyridine, whereas only one tetrahydro base, namely, 4,6-dimethyl-3-piperidine (65), results from 2,4-dimethylpyridine, in addition to the piperidines.<sup>48</sup>

<sup>52</sup> R. R. Rennshaw and R. C. Conn, *J. Am. Chem. Soc.* **60**, 745 (1938).

<sup>53</sup> A. Šilhánková, D. Doskočilová, and M. Ferles, unpublished results.



Ladenburg reduction of 2,4,6-trimethylpyridine affords a mixture of *cis*-2,4,6-trimethyl-3-piperideine (66) and all three isomeric 2,4,6-trimethylpiperidines.<sup>54</sup>



## 2. Electrolytic Reductions

The tetrahydro bases have been mentioned as possible by-products of electrolytic reduction of pyridines in some papers.<sup>55, 56</sup> Davies and McGee<sup>57</sup> isolated 3-piperideine by fractional distillation of crude piperidine obtained by electrolytic reduction of pyridine. Appreciable amounts of 3-piperideines were obtained on reduction of pyridine and its homologs at activated lead electrodes in dilute sulfuric acid.<sup>47</sup> The following tetrahydro bases were isolated (in addition to the corresponding hexahydro bases): 3-piperideine<sup>47</sup> from the reduction of

<sup>54</sup> A. Šilhánková, D. Doskočilová, and M. Ferles, *Collect. Czech. Chem. Commun.* **34**, 1985 (1969).

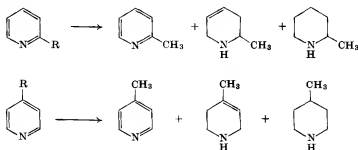
<sup>55</sup> C. Marie and G. Lejeune, *J. Chim. Phys.* **22**, 59 (1925); *Chem. Abstr.* **19**, 1708 (1925).

<sup>56</sup> S. Szmaragd and E. Briner, *Helv. Chim. Acta* **32**, 553 (1949).

<sup>57</sup> W. H. Davies and L. L. McGee, *J. Chem. Soc.*, 678 (1950).

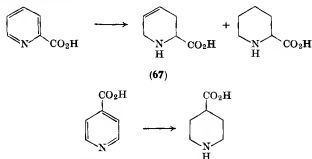
pyridine, 6-methyl-3-piperidine<sup>47</sup> from 2-methylpyridine, 3-methyl-3-piperidine<sup>47</sup> from 3-methylpyridine, 5-isopropyl-3-piperidine<sup>48</sup> from 3-isopropylpyridine, 4-methyl-3-piperidine<sup>47</sup> from 4-methylpyridine, 4-ethyl-3-piperidine<sup>48</sup> from 4-ethylpyridine, 4-isopropyl-3-piperidine<sup>48</sup> from 4-isopropylpyridine, and a mixture<sup>48</sup> of 3-ethyl-3-piperidine and 5-ethyl-3-piperidine (a similar mixture is formed also in the Ladenburg reduction) from 3-ethylpyridine.

Electrolytic reductions of 2- or 4-pyridylmethanol,<sup>58</sup> 4-formylpyridine,<sup>48</sup> and 4-pyridinecarboxylic acid<sup>59, 60</sup> afford mixtures of the corresponding methylpyridine, methyl-3-piperidine, and methylpiperidine.



R = CH<sub>2</sub>OH, CHO, CO<sub>2</sub>H

In addition to the above bases, pipercolinic acid and (±)-baikiaïn<sup>60</sup> (67) are obtained by the electrolytic reduction of picolinic acid, and isonipecotinic acid<sup>59</sup> results from isonicotinic acid. (For a discussion of baikiaïn, see Section V, B.)

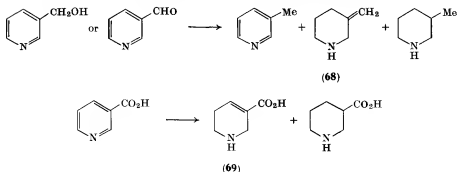


<sup>58</sup> M. Ferles and A. Tesařová, *Collect. Czech. Chem. Commun.* **32**, 1631 (1967).

<sup>59</sup> F. Šorm, *Collect. Czech. Chem. Commun.* **13**, 57 (1948).

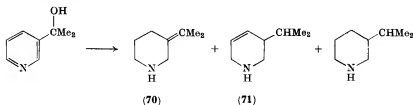
<sup>60</sup> M. Ferles and M. Prystaš, *Collect. Czech. Chem. Commun.* **24**, 3326 (1959).

The interesting formation of 3-methylenepiperidine (68) (along with 3-methylpyridine and 3-methylpiperidine) was observed in the electrolytic reduction of 3-formylpyridine and 3-pyridylcarbinol.<sup>58</sup> Nipecotinic acid and guvacine (69) are obtained from nicotinic acid or its esters.<sup>59</sup> (For a discussion of guvacine, see Section V, A.)



Electrolytic reductions of acetylpyridines<sup>58</sup> afford mixtures of the corresponding ethylpyridines, ethylpiperidines, and ethyl-3-piperideines. Presumably the reductions proceed via the corresponding pyridylmethylcarbinols and ethylpyridines, since a similar mixture of tetrahydro and hexahydro bases was obtained on electrolytic reduction of 3-pyridylmethylcarbinol or 3-ethylpyridine.<sup>61</sup>

A mixture of 3-isopropylidenepiperidine (70), 5-isopropyl-3-piperideine (71), and 3-isopropylpiperidine was obtained in the electrolytic reduction of 3-pyridyldimethylcarbinol. No 3-isopropylpyridine was found in the reaction mixture.<sup>58</sup>



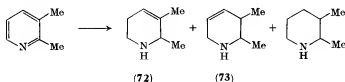
Electrolytic reductions of 2,3-dimethylpyridine,<sup>62</sup> 2,4-dimethylpyridine,<sup>63</sup> 2,5-dimethylpyridine,<sup>62</sup> 3,5-dimethylpyridine,<sup>62</sup> 2-methyl-

<sup>61</sup> M. Ferles and A. Šilhánková, unpublished results.

<sup>62</sup> M. Ferles and A. Šilhánková, *Z. Chem.* **8**, 175 (1968).

<sup>63</sup> J. Lakomý, A. Šilhánková, M. Ferles, and O. Exner, *Collect. Czech. Chem. Commun.* **33**, 1700 (1968).

5-ethylpyridine,<sup>48</sup> 3,4-dimethylpyridine,<sup>62</sup> and 3-methyl-4-ethylpyridine<sup>62</sup> afford mixtures of dialkylpiperidines (usually both stereoisomers) and the corresponding dialkyl-3-piperideines (sometimes both isomers differing in the position of the double bond). These mixtures of products are similar to those obtained in the Ladenburg reduction (see Section II, B, 1). Noteworthy is the electrolytic reduction of 2,3-dimethylpyridine, which affords 2,3-dimethyl-3-piperideine (72), both stereoisomers of 5,6-dimethyl-3-piperideine (73), and 2,3-dimethylpiperidine.<sup>62</sup>



Electrolytic reductions of quaternary pyridinium salts, especially of methyl methosulfates, lead to mixtures of 1-methylpiperidines and

TABLE II

PREPARATION OF 3-PIPERIDEINES BY THE ELECTROLYTIC REDUCTION OF METHYL METHOSULFATES OF PYRIDINE AND SOME OF ITS HOMOLOGS

Methyl methosulfate of:	Product (3-Piperideine)	Reference
Pyridine	1-Methyl-	64
2-Methylpyridine	1,6-Dimethyl-	64, 65
3-Methylpyridine	1,3-Dimethyl-	64, 66
3-Methylpyridine	1,5-Dimethyl-	66
4-Methylpyridine	1,4-Dimethyl-	64
2,3-Dimethylpyridine	1,2,3-Trimethyl-, 1,5,6-trimethyl-	62
2,4-Dimethylpyridine	1,4,6-Trimethyl-, 1,2,4-trimethyl-	65
2,5-Dimethylpyridine	1,3,6-Trimethyl-	62
3,4-Dimethylpyridine	1,3,4-Trimethyl-, 1,4,5-trimethyl-	62
2-Methyl-5-ethylpyridine	1,6-Dimethyl-3-ethyl-	62
3-Methyl-4-ethylpyridine	1,3-Dimethyl-4-ethyl-, 1,5-dimethyl-4-ethyl-	62

<sup>64</sup> M. Ferles, *Collect. Czech. Chem. Commun.* **24**, 2221 (1959).

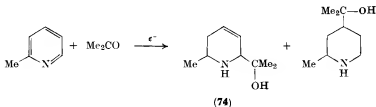
<sup>65</sup> M. Holík, A. Tesařová, and M. Ferles, *Collect. Czech. Chem. Commun.* **32**, 1730 (1967).

<sup>66</sup> M. Ferles and M. Holík, *Collect. Czech. Chem. Commun.* **31**, 2416 (1966).

1-methyl-3-piperideines. The tetrahydro bases are analogous to those obtained by electrolytic reductions of pyridine and its homologs (see Table II). The preparative importance of electrolytic reductions of quaternary salts of pyridines is small since the hexahydro bases predominate in the resulting mixtures of products.

### 3. Mixed Electrolytic Reduction of Pyridine Bases and Ketones

Preparation of secondary (or tertiary) carbinols from pyridines and an aldehyde (or a ketone) in the presence of magnesium or aluminum and mercuric chloride is known in pyridine chemistry as the Emmert reaction.<sup>67-70</sup> For example, dimethyl-2-pyridylcarbinol is obtained in this way from pyridine and acetone. When a mixture of pyridine and acetone is subjected to an electrolytic reduction in dilute sulfuric acid at lead electrodes, a mixture of two main products results, namely, 2-(2-hydroxy-2-propyl)-3-piperideine and 4-(2-hydroxy-2-propyl)piperidine. Analogous compounds are obtained with the use of methyl ethyl ketone as the reactant. The mixed electrolytic reduction of 2-methylpyridine and acetone affords 2-(2-hydroxy-2-propyl)-6-methyl-3-piperideine (74) and 2-methyl-4-(2-hydroxy-2-propyl)piperidine.<sup>71</sup>



The mixed electrolytic reduction of pyridines substituted at position 4 leads exclusively to the unsaturated amino alcohols (e.g., 75).<sup>71</sup>

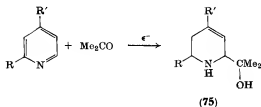
<sup>67</sup> B. Emmert and E. Asendorf, *Ber.* **72**, 1188 (1939).

<sup>68</sup> B. Emmert and E. Pirot, *Ber.* **74**, 714 (1941).

<sup>69</sup> H. L. Lochte, P. F. Kruse, Jr., and E. N. Wheeler, *J. Am. Chem. Soc.* **75**, 4477 (1953).

<sup>70</sup> G. B. Bachman, M. Hamer, E. Dunning, and R. M. Schisla, *J. Org. Chem.* **22**, 1296 (1957).

<sup>71</sup> M. Ferles, M. Vanka, and A. Šilhánková, *Collect. Czech. Chem. Commun.* **34**, 2108 (1969).

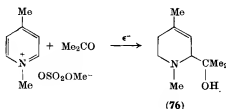


R = H, R' = Me

R = R' = Me

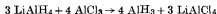
2,4,6-Trimethylpyridine, with all the critical positions blocked, does not undergo mixed electrolytic reduction with ketones.<sup>61</sup>

The mixed electrolytic reduction has been performed also with quaternary salts of pyridine<sup>71</sup> and its homologs<sup>72</sup> and acetone or some other ketones. 1,4-Dimethyl-2-(2-hydroxy-2-propyl)-3-piperidineine (76) was formed from 1,4-dimethylpyridinium methosulfate and acetone.<sup>71</sup>



#### 4. Reductions with Aluminum Hydride

As shown by Schlesinger *et al.*,<sup>73</sup> treatment of an ethereal solution of aluminum chloride with excess lithium aluminum hydride leads to the formation of aluminum hydride which may be used *in situ* in reductions of a variety of nitrogen compounds.<sup>74, 75</sup> In these reductions, aluminum hydride shows a similar reductive ability as lithium aluminum hydride.



<sup>72</sup> M. Ferles and J. Vymětal, unpublished results.

<sup>73</sup> A. E. Finholt, A. C. Bond, Jr., and H. I. Schlesinger, *J. Am. Chem. Soc.* **69**, 1199 (1947).

<sup>74</sup> E. Wiberg and M. Schmidt, *Z. Naturforsch.* **6b**, 333 (1951).

<sup>75</sup> M. Ferles, *Z. Chem.* **6**, 224 (1966).

The electrophilic character of aluminum hydride is particularly suitable in reductions of pyridine bases. As shown in the following scheme, the addition of aluminum hydride to the nitrogen of the heterocycle is followed by an intramolecular or intermolecular reduc-

TABLE III

PREPARATION OF 3-PIPERIDEINES BY THE ALUMINUM HYDRIDE REDUCTION OF PYRIDINE AND ITS HOMOLOGS

Starting base	Product	Reference
Pyridine	3-Piperidine	76
3-Methylpyridine	3-Methyl-3-piperidine	76
4-Methylpyridine	4-Methyl-3-piperidine	76
2,3-Dimethylpyridine	2,3-Dimethyl-3-piperidine, 5,6-dimethyl-3-piperidine	77
2,4-Dimethylpyridine	4,6-Dimethyl-3-piperidine	77
2,5-Dimethylpyridine	3,6-Dimethyl-3-piperidine	77
3,4-Dimethylpyridine	3,4-Dimethyl-3-piperidine, 4,5-dimethyl-3-piperidine	77
3,5-Dimethylpyridine	3,5-Dimethyl-3-piperidine	77
3-Ethylpyridine	3-Ethyl-3-piperidine, 5-ethyl-3-piperidine	48
4-Ethylpyridine	4-Ethyl-3-piperidine	48
3-Methyl-4-ethylpyridine	3-Methyl-4-ethyl-3-piperidine, 4-ethyl-5-methyl-3-piperidine	77
2-Methyl-5-ethylpyridine	3-Ethyl-6-methyl-3-piperidine	48
3-Isopropylpyridine	5-Isopropyl-3-piperidine	48
4-Isopropylpyridine	4-Isopropyl-3-piperidine	48

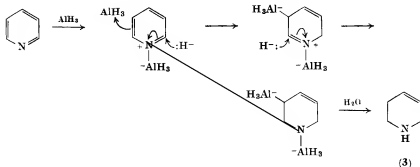
tion of the imine grouping, addition of a further molecule of aluminum hydride to position 3, and reduction of the new imine grouping resulting from a shift of the electron pair of the nitrogen atom. The final decomposition with water leads to 3-piperidine (3).

The aluminum hydride reduction of pyridine bases is very advantageous in the preparation of 3-piperideines since the amount of the corresponding accompanying hexahydro bases is small. The resulting tetrahydropyridines possess the same constitution as those obtained by the electrolytic or Ladenburg reduction (see Table III).

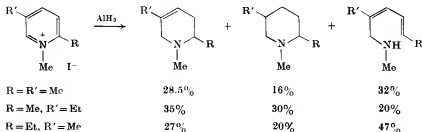
<sup>76</sup> M. Ferles, *Sci. Papers Inst. Chem. Technol. Prague, C* **4**, 519 (1960); *Chem. Abstr.* **55**, 24740 (1961).

<sup>77</sup> A. Šilhánková, M. Holík, and M. Ferles, *Collect. Czech. Chem. Commun.* **33**, 2494 (1968).





Somewhat less useful is the aluminum hydride reduction of quaternary pyridinium salts. Reduction of the salts may be more conveniently performed by the use of sodium borohydride (see Section II, B, 6). Moreover, the aluminum hydride reductions of some dialkylpyridinium salts are accompanied by reductive cleavage of the pyridine ring.<sup>77</sup> For example, methiodides of 2,5-dimethylpyridine,<sup>77</sup> 2-methyl-5-ethylpyridine,<sup>77</sup> and 2-ethyl-5-methylpyridine<sup>61</sup> afford mixtures of the corresponding tetrahydro and hexahydro bases along with a secondary amine, viz., 5-methylaminomethyl-2,4-hexadiene, 5-methylaminomethyl-2,4-heptadiene, and 7-methylamino-6-methyl-2,4-heptadiene, respectively.

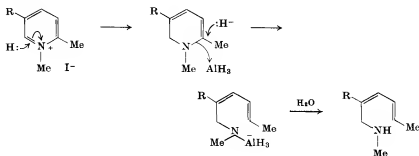


The aluminum hydride reduction of 2,6-dimethylpyridine methiodide is also accompanied by a ring cleavage to a secondary amine.<sup>61</sup>

Formation of methylaminoalkadienes might be explained invoking a 1,2-dihydropyridine intermediate and its cleavage by aluminum hydride, by analogy with the cleavage of enamines.<sup>79</sup>

<sup>78</sup> M. Holík and M. Ferles, *Collect. Czech. Chem. Commun.* **32**, 3067 (1967).

<sup>79</sup> J. M. Coulter, J. W. Lewis, and P. P. Lynch, *Tetrahedron* **24**, 4489 (1968).



### 5. Formic Acid Reduction (The Lukeš Reduction)

Reduction of quaternary pyridinium halides (or, more precisely, formates) with formic acid in the presence of potassium formate at about  $150^\circ\text{C}$  is usually referred to as the Lukeš reduction.<sup>80-95</sup> Instead of potassium formate, triethylamine may be used, especially with quaternary pyridinium iodides.<sup>85, 86</sup> Mixtures of 1-alkyl-3-piperideines (77) and 1-alkylpiperidines (78) are usually obtained. Formation of piperideines (77) might be explained by analogy with the Ladenburg reduction of pyridine bases; the double bond at position 3 is resistant toward further reduction by formic acid or by

<sup>80</sup> J. Pliml, *Chemie* (Prague) **10**, 891 (1958); O. Červinka, *Chem. Listy* **59**, 1058 (1965).

<sup>81</sup> R. Lukeš, *Collect. Czech. Chem. Commun.* **12**, 71 (1947).

<sup>82</sup> R. Lukeš and J. Pliml, *Collect. Czech. Chem. Commun.* **15**, 463 (1950).

<sup>83</sup> R. Lukeš and J. Pliml, *Collect. Czech. Chem. Commun.* **24**, 2560 (1959).

<sup>84</sup> R. Lukeš and M. Ferles, *Collect. Czech. Chem. Commun.* **22**, 121 (1957).

<sup>85</sup> L. G. Yudin, A. N. Kost, Yu. A. Berlin, and A. E. Shipov, *Zh. Obshch. Khim.* **27**, 3021 (1957); *Chem. Abstr.* **52**, 8142 (1958).

<sup>86</sup> A. N. Kost, L. G. Yudin, and A. E. Shipov, *Vestn. Mosk. Univ. Ser. Khim.* **11**, No. 1, 209 (1956); *Chem. Abstr.* **52**, 9114 (1958).

<sup>87</sup> R. Lukeš and J. Jizba, *Collect. Czech. Chem. Commun.* **19**, 941 (1954).

<sup>88</sup> M. Ferles and Z. Vondráčková, unpublished results.

<sup>89</sup> R. Lukeš and M. Ferles, *Collect. Czech. Chem. Commun.* **22**, 121 (1957).

<sup>90</sup> R. Lukeš and J. Pliml, *Collect. Czech. Chem. Commun.* **21**, 638 (1956).

<sup>91</sup> R. Lukeš, J. Jizba, J. Pliml, and V. Štěp, *Collect. Czech. Chem. Commun.* **19**, 949 (1954).

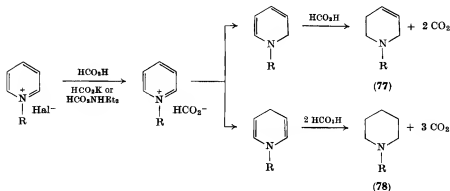
<sup>92</sup> R. Lukeš and J. Pliml, *Collect. Czech. Chem. Commun.* **21**, 1602 (1956).

<sup>93</sup> R. Lukeš, J. N. Zvonkova, A. F. Mironov, and M. Ferles, *Collect. Czech. Chem. Commun.* **25**, 2668 (1960).

<sup>94</sup> R. Lukeš and J. Jizba, *Collect. Czech. Chem. Commun.* **19**, 930 (1954).

<sup>95</sup> O. Červinka and O. Kříž, *Collect. Czech. Chem. Commun.* **30**, 1700 (1965).

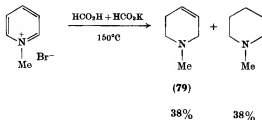
sodium in alcohols, but may be saturated by catalytic hydrogenation (cf. Section II, B, 1).



R = Me, Et, Pr, Bu, iso-Am, PhCH<sub>2</sub>, Ph

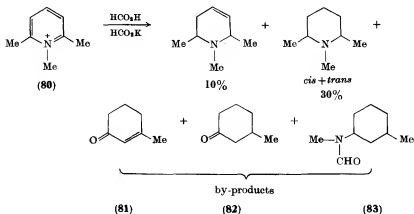
Hal = Cl, Br, I

The Lukeš reduction of 1-methylpyridinium bromide affords a 76% yield of a 1:1 mixture of 1-methyl-3-piperidine (79) and 1-methylpiperidine.<sup>81</sup>

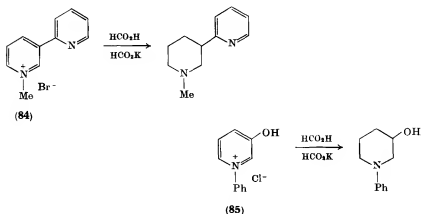


In Lukeš reductions of quaternary salts of pyridine homologs, the ratio of the tetrahydro to the hexahydro product is strongly dependent of the position and bulkiness of the substituent on the pyridine ring. Only the tetrahydro base is obtained from 4-methylpyridine methobromide.<sup>83</sup> On the other hand, both the tetrahydro and hexahydro bases (in the ratio 1:1) result from the reduction of 3-methylpyridine methobromide.<sup>82</sup> The Lukeš reductions of 2-methylpyridine methobromide and 2,6-dimethylpyridine methobromide (80) are accompanied by formation of by-products (81–83) due to reductive cleavage

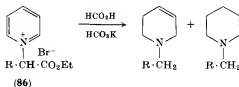
of the pyridine ring (probably at the 1,4-dihydro stage) and cyclization.<sup>87</sup>



Only hexahydro bases were isolated in the Lukeš reduction of 1-methyl-3,2'-dipyridylium bromide<sup>90</sup> (84) and 1-phenyl-3-hydroxypyridinium chloride (85).<sup>89</sup>

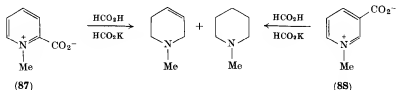


The Lukeš reduction of 1-(ethoxycarbonylmethyl)pyridinium bromide (86, R = H) and 1-(1-ethoxycarbonyl-ethyl)pyridinium bromide (86, R = Me) was accompanied by decarboxylation; mixtures of the appropriate 1-methyl- or 1-ethyl-piperidine and 3-piperideine were obtained.<sup>92</sup>

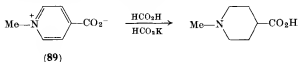


R = H, Me

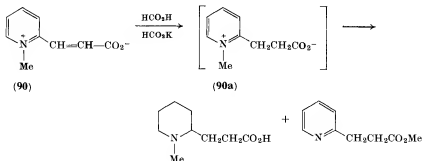
Decarboxylations occurred also in the Lukeš reduction of the methyl betaines of picolinic and nicotinic acids. Thus, both homarine (87) and trigonelline (88) afforded a mixture of 1-methyl-3-piperidine and 1-methylpiperidine.<sup>91</sup>



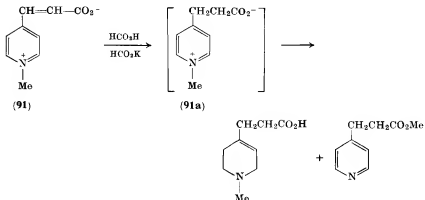
In contrast, the Lukeš reduction of isonicotinic acid methyl betaine (89) afforded 1-methylisonipecotinic acid.<sup>91</sup>



The methyl betaines of 3-(2-pyridyl)acrylic acid (90) and 3-(4-pyridyl)acrylic acid (91) behave slightly differently on Lukeš reduction. A piperidine derivative results in the former case (90), and a



3-piperideine derivative is formed from the methyl betaine (91). The concomitant occurrence of methyl 3-(2-pyridyl)propionate and methyl 3-(4-pyridyl)propionate might be due to thermal rearrangement of the hypothetical intermediates (90a and 91a).<sup>93</sup>



Červinka and Kříž<sup>95</sup> investigated the mechanism of the Lukeš reduction with the use of deuteriated formic acid. 1-Methylpyridinium iodide afforded a mixture of 1-methyl-5-deuterio-3-piperideine (92, R = H) and 1-methyl-3,5-dideuteriopiperidine (93, R = H). A mixture containing 1,3-dimethyl-3,5-dideuteriopiperidine (93, R = Me) was obtained from 1,3-dimethylpyridinium iodide.

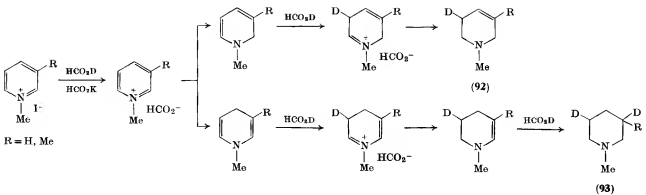
According to their proposal, the reduction is effected by hydride ion transfer from the formate anion which, as a nucleophile, reacts at positions 2, 4, or 6 where the electron density is lowest (cf. calculations by the HMO method<sup>96, 97</sup>) to give the 1,2-dihydro and 1,4-dihydro intermediates. Further reduction of the 1,2-dihydro compound leads to the 3-piperideine (92), whereas the hexahydro derivative (93) is obtained from the 1,4-dihydro intermediate.

### 6. Complex Metal Hydride Reduction

Reductions of quaternary pyridinium salts to 1-alkyl-3-piperideines may be performed preferably with the use of sodium or potassium borohydride in aqueous or alcoholic solutions. Lithium aluminum

<sup>96</sup> J. Kuthan, J. Paleček, J. Procházková, and V. Skála, *Collect. Czech. Chem. Commun.* **33**, 3138 (1968).

<sup>97</sup> R. Zahradník and C. Parkányi, *Collect. Czech. Chem. Commun.* **30**, 355 (1965).

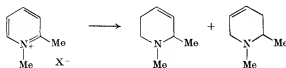


hydride appears to be less suitable in these reductions (a powdered quaternary salt or its chloroform solution is added to an ethereal solution of lithium aluminum hydride).<sup>64</sup> Sodium aluminum hydride has been used only exceptionally.<sup>98</sup> Reductions of quaternary pyridinium salts with complex hydrides were reviewed in Volume 6 of *Advances in Heterocyclic Chemistry* by Lyle and Anderson.<sup>99</sup>

In contrast to aluminum hydride reductions (see Section II, B, 4), no ring openings have been observed in reductions of quaternary pyridinium salts by means of sodium borohydride. Whenever possible, both isomeric tetrahydropyridines are formed, as it may be seen from the following examples (aluminum hydride, electrolytic, and formic acid reductions are included for comparison).



X	Reagent	Yield (%)	Ref.
I	NaBH <sub>4</sub>	87.5	100
I	LiAlH <sub>4</sub>	100	101
I	AlH <sub>3</sub>	97	101
OSO <sub>3</sub> Me	Electroreduction	19	64
Br	HCO <sub>2</sub> H + HCO <sub>2</sub> K	38	81



X	Reagent	Yield (%)	Ref.
I	NaBH <sub>4</sub>	13 84	101
I	LiAlH <sub>4</sub>	39 61	101
I	AlH <sub>3</sub>	37 57	101
OSO <sub>3</sub> Me	Electroreduction	— 22	64
Br	HCO <sub>2</sub> H + HCO <sub>2</sub> K	— 17	87

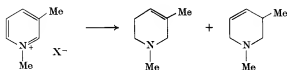
<sup>98</sup> M. Ferles, unpublished results.

<sup>99</sup> R. E. Lyle and P. S. Anderson, *Advan. Heterocycl. Chem.* **6**, 45 (1966).

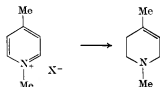
<sup>100</sup> M. Ferles, *Collect. Czech. Chem. Commun.* **23**, 479 (1958).

<sup>101</sup> M. Holík and M. Ferles, *Collect. Czech. Chem. Commun.* **32**, 3067 (1967).

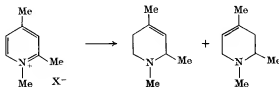




X	Reagent	Yield (%)		Ref.
I	NaBH <sub>4</sub>	91.5	5	66
I	LiAlH <sub>4</sub>	84.5	15.5	66
I	KBH <sub>4</sub>	82.5	7.5	66
I	AlH <sub>3</sub>	84	16	101
OSO <sub>3</sub> Me	Electroreduction	48.5	8.5	66
I	HCO <sub>2</sub> H + HCO <sub>2</sub> K	48.5	8.5	66

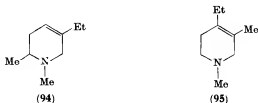


X	Reagent	Yield (%)		Ref.
I	NaBH <sub>4</sub>	97.5		100
I	LiAlH <sub>4</sub>	100		101
I	AlH <sub>3</sub>	100		101
OSO <sub>3</sub> Me	Electroreduction	50		66
Br	HCO <sub>2</sub> H + HCO <sub>2</sub> K	84		83

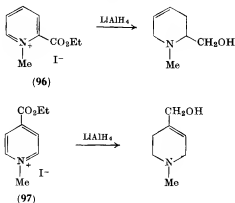


X	Reagent	Yield (%)		Ref.
I	NaBH <sub>4</sub>	27	73	65
I	LiAlH <sub>4</sub>	66	34	101
I	AlH <sub>3</sub>	46	54	101
OSO <sub>3</sub> Me	Electroreduction	1	75	65

In addition to compounds quoted by Lyle and Anderson,<sup>99</sup> the following quaternary salts have recently been reduced with sodium borohydride: ethiodides of pyridine and its homologs, methiodides of 3-ethylpyridine, 4-ethylpyridine, 2-methyl-5-ethylpyridine, and 3-methyl-4-ethylpyridine,<sup>102</sup> and the methiodide of 2-benzyl-4-methylpyridine.<sup>103</sup> Reductions ( $\text{NaBH}_4$ ) of 1,2-dimethyl-5-ethylpyridinium iodide and 1,3-dimethyl-4-ethylpyridinium iodide afford as principal products those 3-piperideines (**94**, **95**) which carry the maximum number of substituents on the double bond, presumably due to hyperconjugation.<sup>102</sup>



Treatment of ethyl picolinate methiodide<sup>60</sup> (**96**) and ethyl isonicotinate methiodide<sup>64</sup> (**97**) with lithium aluminum hydride results in reduction of both the pyridine ring and the attached functional group.

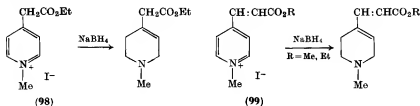


On the other hand, with sodium borohydride, only the pyridine ring of compounds **96** and **97** undergoes reduction. Similar results

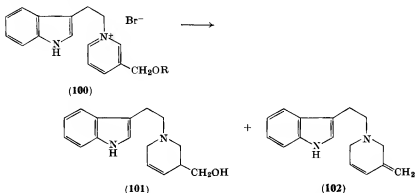
<sup>102</sup> M. Ferles, M. Kovařík, and Z. Vondráčková, *Collect. Czech. Chem. Commun.*, **31**, 1348 (1966).

<sup>103</sup> J. Plíml, *Collect. Czech. Chem. Commun.*, **26**, 3039 (1961).

were obtained on sodium borohydride reduction of ethyl 4-pyridylacetate methiodide<sup>98</sup> (**98**) and ethyl or methyl 3-(4-pyridyl)acrylate<sup>105</sup> (**99**).



The sodium borohydride reduction of 1-[β-(3-indolyl)ethyl]-3-hydroxymethylpyridinium bromide (**100**, R = H) affords a 73% yield of the 3-piperidine (**101**), but with the use of lithium aluminum hydride a 50% yield of the diene (**102**) is obtained. The lithium tri-*t*-butoxy aluminum hydride reduction of (**100**) leads to a mixture



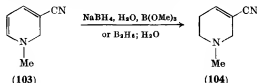
R	Reagent	Yield (%)	
		(101)	(102)
H	NaBH <sub>4</sub>	73	—
H	LiAlH <sub>4</sub>	—	50
H	Li( <i>t</i> -BuO) <sub>3</sub> AlH	28	18
Ac	NaBH <sub>4</sub>	—	30
Ac	LiAlH <sub>4</sub>	—	45
Ac	Li( <i>t</i> -BuO) <sub>3</sub> AlH	—	31

<sup>104</sup> M. Holík and M. Ferles, *Collect. Czech. Chem. Commun.* **32**, 2288 (1967).

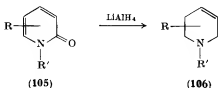
<sup>105</sup> A. Mironov, M. Ferles, and M. Pergál, *Sci. Papers Inst. Chem. Technol. Prague, Ser. Org. Technol.* **5**, 83 (1961).

of **101** (28%) and **102** (18%). Exclusive formation of the diene (**102**) was observed in the reduction of the acetate (**100**, R = Ac) with all the above reducing agents.<sup>106</sup> For reductions of quaternary salts of 4-(3-indolyl)pyridine with sodium borohydride in aqueous methanol, see Section IV, A.

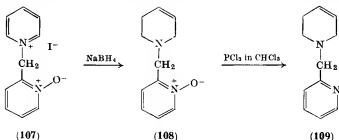
Reduction of 1-methyl-3-cyano-1,2-dihydropyridine (**103**) with sodium borohydride in the presence of trimethyl borate, or with externally generated  $B_2H_6$ , has recently been reported to yield 1-methyl-3-cyano-3-piperidine (**104**) quantitatively.<sup>107</sup>



Low yields of 1-alkyl-3-piperideines (**106**) result on reduction of 1-alkyl-2-pyridones (**105**) with lithium aluminum hydride or a mixed hydride obtained by reaction of lithium aluminum hydride and aluminum chloride in a 1:1 ratio.<sup>65, 66, 104</sup>



1-(2-Pyridylmethyl)-3-piperidine (**109**) may be obtained by the action of phosphorus trichloride on the corresponding *N*-oxide (**108**)



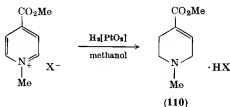
<sup>106</sup> F. E. Ziegler and J. G. Sweeny, *J. Org. Chem.* **32**, 3216 (1967).

<sup>107</sup> F. Liberatore, V. Carelli, and M. Cardellini, *Tetrahedron Letters* 4735 (1968).

which, in turn, arises on sodium borohydride reduction of 1-(*N*-oxidopyridylmethyl)pyridinium iodide (**107**).<sup>108</sup>

### 7. Catalytic Hydrogenation

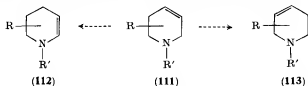
Catalytic hydrogenation may be used in the preparation of 3-piperideines only exceptionally, e.g., in the case of some 4-substituted pyridines as the starting compounds, since usually the catalytic hydrogenation of pyridine, its homologs, derivatives, and quaternary salts leads to the hexahydro compounds. 1-Methyl-4-methoxycarbonyl-3-piperideine hydrohalide (**110**), however, was obtained by hydrogenation of methyl isonicotinate methiodide<sup>109, 110</sup> or methobromide<sup>110</sup> over platinum dioxide in methanol.



## III. Properties

3-Piperideines are for the most part stable liquids distillable at ordinary pressure or *in vacuo*. Some of the higher members of the 3-piperideine series are crystalline. Some 4-substituted 3-piperideines may be somewhat unstable in air.

From the theoretical point of view, 3-piperideines (**111**) could isomerize into 2-piperideines (**112**) or 4-piperideines (**113**).

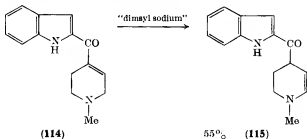


<sup>108</sup> M. Hamana, B. Umezawa, and K. Noda, *Chem. Pharm. Bull. (Tokyo)* **11**, 694 (1963).

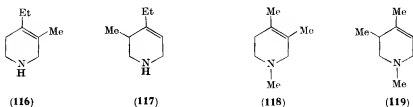
<sup>109</sup> J. V. Supniewsky and M. Serafinówna, *Arch. Chem. Farm.* **3**, 109 (1936); *Chem. Abstr.* **33**, 7301 (1939).

<sup>110</sup> (a) R. E. Lyle, E. F. Perłowski, H. J. Troscianiec, and G. G. Lyle, *J. Org. Chem.* **20**, 1761 (1955); (b) R. E. Lyle and S. E. Mallett, *Ann. N.Y. Acad. Sci.* **145**, 83 (1967).

To our knowledge, no isomerizations of 3-piperideines (**111**) to the enamines (**112**) have been observed in alkaline media,<sup>98, 111</sup> except for a preliminary communication on the so-called deconjugation of 1-methyl-4-(2-indolylcarbonyl)-3-piperideine (**114**) to the enamine (**115**) by the action of "dimethyl sodium."<sup>112</sup>



Concerning the other possibility, the isomerization of 3-piperideines (**111**) to 4-piperideines (**113**), the mixtures of 3-methyl-4-ethyl-3-piperideine (**116**) and 4-ethyl-5-methyl-3-piperideine (**117**), and of 1,3,4-trimethyl-3-piperideine (**118**) and 1,4,5-trimethyl-3-piperideine (**119**) were found to be quite stable to the prolonged action of dilute sulfuric acid (conditions of electrolytic reduction), dilute alkali (conditions of isolation procedures), sodium alkoxides (conditions of the Ladenburg reduction), and aluminum hydride.<sup>61</sup>



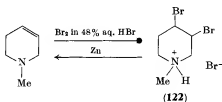
Recently,<sup>10</sup> the stabilities of 1-benzyl-3-methyl-4-phenyl-3-piperideine (**120**) and 1-benzyl-4-phenyl-5-methyl-3-piperideine (**121**) were investigated under forcing conditions, namely, by refluxing a pure isomer in a mixture of concentrated hydrochloric acid and acetic acid

<sup>111</sup> E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, and M. Terashima, *J. Org. Chem.* **33**, 747 (1968).

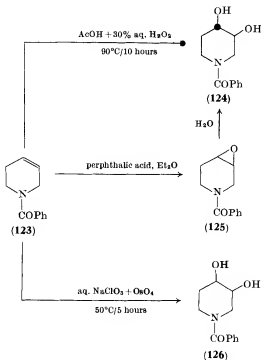
<sup>112</sup> A. Jackson and J. A. Joule, *Chem. Commun.*, 459 (1967).



separate mixtures of 3-piperideines and the corresponding piperidines; these mixtures result after reductions of pyridines<sup>43, 44, 76</sup> or their quaternary salts<sup>71, 81, 102</sup> (cf. Section II, B, 1). Treatment of 1-methyl-3-piperideine with bromine in hydrobromic acid leads to 1-methyl-3,4-dibromopiperidine hydrobromide (122), from which the parent compound may be recovered by the action of zinc.<sup>81</sup>



The *trans*-hydroxylation of 1-benzoyl-3-piperideine (123) with peracetic acid led to *trans*-1-benzoylpiperidine-3,4-diol (124).<sup>113</sup> With



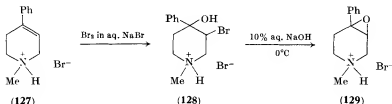
<sup>113</sup> V. Petrow and O. Stephenson, *J. Pharm. Pharmacol.* **14**, 306 (1962).



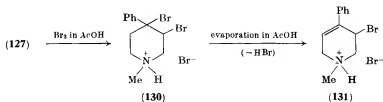
etheral perphthalic acid, **123** gave 1-benzoyl-3,4-epoxypiperidine (**125**) which yielded the trans-diol (**124**) on hydration.<sup>113</sup>

The cis-hydroxylation of **123** to *cis*-1-benzoylpiperidine-3,4-diol (**126**) was readily accomplished with the use of aqueous sodium chlorate-osmium tetroxide at 50°–60°C.<sup>113</sup>

Addition of hypobromous acid to 1-methyl-4-phenyl-3-piperidine hydrobromide (**127**) was accomplished by the action of bromine in aqueous sodium bromide. Treatment of the resulting 1-methyl-3-bromo-4-phenyl-4-piperidinol hydrobromide (**128**) with 10% aqueous sodium hydroxide gave 1-methyl-4-phenyl-3,4-epoxypiperidine (**129**).<sup>114</sup> (Compound **128** was formerly given the erroneous structure of 1-methyl-5-bromo-4-phenyl-3-piperidine hydrobromide.<sup>7</sup>)



Evaporation of an acetic acid solution of 1-methyl-3,4-dibromo-4-phenylpiperidine hydrobromide (**130**) (obtained from **127** by addition of bromine in acetic acid) was unexpectedly accompanied by dehydrobromination, with the formation of 1-methyl-4-phenyl-5-bromo-3-piperidine hydrobromide (**131**).<sup>115</sup>



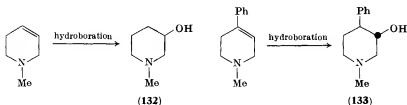
Hydroboration of 1-methyl-3-piperidine with (–)-diisopinocampheylborane (followed by oxidation) gave (–)-*S*-1-methyl-3-piperidinol (**132**).<sup>116</sup> A similar hydroboration of 1-methyl-4-phenyl-3-

<sup>114</sup> R. E. Lyle and W. E. Krueger, *J. Org. Chem.* **30**, 394 (1965).

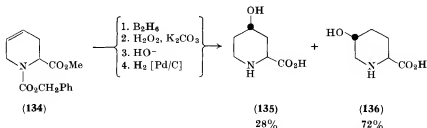
<sup>115</sup> R. E. Lyle and W. E. Krueger, *J. Org. Chem.* **32**, 3613 (1967).

<sup>116</sup> C. K. Spicer, *Dissertation Abstr.* **B27**, 2659 (1966).

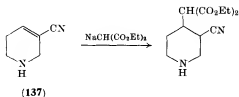
piperideine afforded *trans*-1-methyl-4-phenyl-3-piperidinol (**133**).<sup>116, 117</sup>



The hydroboration of (±)-baikiain (4,5-dehydro-(±)-pipecolic acid) via its *N*-benzyloxycarbonyl methyl ester derivative (**134**) led, after oxidation and removal of the protecting groups, to 72% *trans*-5-hydroxy-(±)-pipecolic acid (**136**) and 28% *trans*-4-hydroxy-(±)-pipecolic acid (**135**), separable by preparative ion-exchange column chromatography.<sup>118</sup>



Addition of diethyl sodiomalonate to the double bond was accomplished in the case of 3-cyano-3-piperideine (**137**).<sup>119</sup>



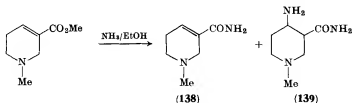
Addition of ammonia to the double bond accompanied the reaction of arecaidine with alcoholic ammonia. A mixture of 1-methyl-1,2,5,6-

<sup>117</sup> R. E. Lyle, D. H. McMahon, W. E. Krueger, and C. K. Spicer, *J. Org. Chem.* **31**, 4164 (1966).

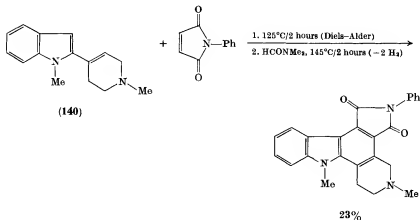
<sup>118</sup> Y. Fujita, F. Irreverre, and B. Witkop, *J. Am. Chem. Soc.* **86**, 1844 (1964).

<sup>119</sup> A. Wohl and M. S. Losanitsch, *Ber.* **40**, 4698 (1907).

tetrahydronicotinamide (**138**) and 1-methyl-4-aminonipicotinamide (**139**) resulted.<sup>120</sup>



Treatment of 1-methyl-4-(1-methyl-2-indolyl)-3-piperideine (**140**) with maleic acid *N*-phenylimide in the presence of hydroquinone results in a Diels–Alder cycloaddition which is followed by dehydrogenation.<sup>121</sup> The 1-methyl-3-indolyl analog of **140** reacted similarly.<sup>121</sup>



## B. REACTIONS INVOLVING THE RING NITROGEN

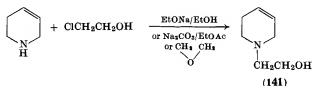
Alkylation of 3-piperideines at the nitrogen atom is usually performed by the action of alkyl halides on the corresponding sodium derivatives. Thus, 1-(2-hydroxyethyl)-3-piperideine (**141**) was obtained from ethylene chlorohydrin and 3-piperideine pretreated with sodium ethoxide in ethanol,<sup>122</sup> or by refluxing a mixture of 3-piperi-

<sup>120</sup> P. Karrer and H. Ruckstuhl, *Helv. Chim. Acta* **27**, 1698 (1944).

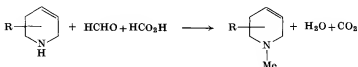
<sup>121</sup> D. Beck and K. Schenker, *Helv. Chim. Acta* **51**, 260, 264 (1968).

<sup>122</sup> P. Chabrier, H. Najer, R. Giudicelli, and M. Joannic, *Bull. Soc. Chim. France*, 1365 (1965).

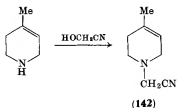
deine, ethylene chlorohydrin, and sodium carbonate in ethyl acetate.<sup>126</sup> Compound **141** may also be obtained using ethylene oxide.<sup>113</sup>



Methylation of 3-piperideines can be performed by the Eschweiler-Clarke reaction (treatment with formaldehyde in the presence of excess formic acid).<sup>54</sup>



1-Cyanomethyl-4-methyl-3-piperideine (**142**), the intermediate in the preparation of 1-(2-guanidinoethyl)-4-methyl-3-piperideine (see Section VI, Lerone), was obtained from 4-methyl-3-piperideine by the action of hydroxyacetonitrile.<sup>123</sup> The homologous 1-cyanomethyl-4,6-dimethyl-3-piperideine was prepared with the use of chloroacetonitrile.<sup>124</sup>

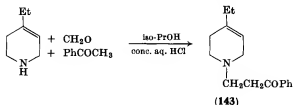


The Mannich reaction of 4-ethyl-3-piperideine with formaldehyde and acetophenone gave 1-(2-benzoyl-ethyl)-4-ethyl-3-piperideine (**143**).<sup>125</sup>

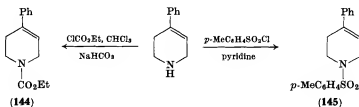
<sup>123</sup> Farbenfabriken Bayer A.G., French Patent M3016 (1965); *Chem. Abstr.* **62**, 16206 (1965).

<sup>124</sup> M. Ferles, A. Šilhánková, and A. Dlabač, Czechoslovak Patent 133,308 (1969).

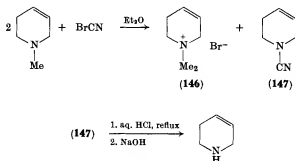
<sup>125</sup> P. A. J. Janssen, U.S. Patent 3,030,372 (1962); *Chem. Abstr.* **59**, 2780 (1963).



Acylation<sup>113, 126, 127</sup> of 3-piperideines may be illustrated by the preparation of 1-ethoxycarbonyl-4-phenyl-3-piperideine (144) and 1-*p*-toluenesulfonyl-4-phenyl-3-piperideine (145).



Demethylation of 1-methyl-3-piperideines may be accomplished with the use of the von Braun cyanogen bromide procedure.<sup>60, 128</sup> A certain drawback of this method consists in loss of half of the tertiary amine in formation of a quaternary salt (e.g., 146), in addition to the required 1-cyano derivative (e.g., 147), which is then hydrolyzed to the required secondary amine. 3-Piperideine was obtained by this procedure in the form of a stable free base.<sup>128</sup>



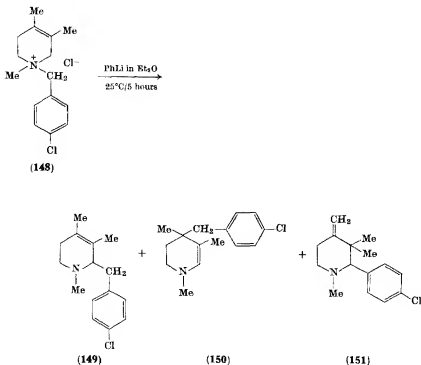
<sup>126</sup> A. F. Casy and H. Birnbaum, *J. Chem. Soc. C*, 64 (1966).

<sup>127</sup> D. Taub, C. H. Kuo, and N. L. Wendler, *J. Chem. Soc. C*, 1558 (1967).

<sup>128</sup> R. Lukeš and J. Pliml, *Collect. Czech. Chem. Commun.* **19**, 502 (1954).

Similar to 1-alkylpiperidines, 1-alkyl-3-piperideines may readily be quaternized by the action of various alkyl halides.

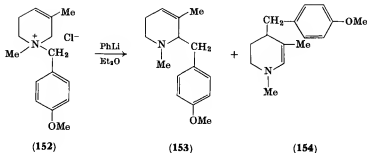
The Stevens rearrangement of 1,3,4-trimethyl-1-*p*-chlorobenzyl-3-piperideinium chloride (148) with phenyllithium in ether was found to give three products, namely, 15% 1,3,4-trimethyl-2-*p*-chlorobenzyl-3-piperideine (149), 1,3,4-trimethyl-4-*p*-chlorobenzyl-2-piperideine (150), and 1,3,3-trimethyl-2-*p*-chlorophenyl-4-methylenepiperidine (151).<sup>129a</sup>



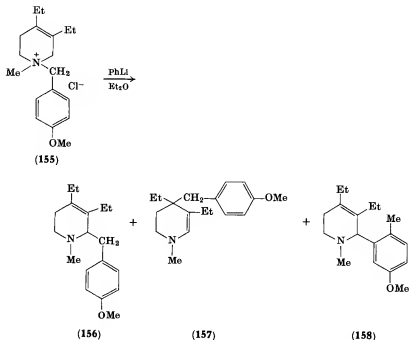
Similar treatment of 1,3-dimethyl-1-*p*-methoxybenzyl-3-piperideinium chloride (152) (with an unoccupied 4-position) gave a mixture of 1,3-dimethyl-2-*p*-methoxybenzyl-3-piperideine (153) and 1,3-dimethyl-4-*p*-methoxybenzyl-2-piperideine (154).<sup>129b</sup>

<sup>129a</sup> A. E. Jacobson, *J. Org. Chem.* **31**, 1569 (1966).

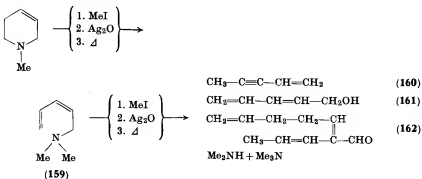
<sup>129b</sup> A. E. Jacobson and T. R. Parfitt, *J. Org. Chem.* **32**, 1894 (1967).



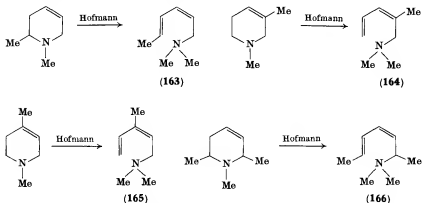
A mixture of 1-methyl-2-*p*-methoxybenzyl-3,4-diethyl-3-piperideine (156), 1-methyl-3,4-diethyl-4-*p*-methoxybenzyl-2-piperideine (157), and 1-methyl-2-(2-methyl-5-methoxyphenyl)-3,4-diethyl-3-piperideine (158) was obtained from 1-methyl-1-*p*-methoxybenzyl-3,4-diethyl-3-piperideinium chloride (155). Compounds 156 and 157 were formed by the Stevens rearrangement, whereas the formation of compound 158 was due to the Sommelet rearrangement.<sup>129b</sup>



In analogy to piperidines, some 3-piperideines were subjected to the Hofmann exhaustive methylation. 5-Dimethylamino-1,3-pentadiene (159) was obtained from 1-methyl-3-piperideine.<sup>81</sup> Repetition of the Hofmann procedure led to the formation of pirylyene (160), 2,4-pentadien-1-ol (161), 2-(1-propenyl)-2,6-heptadienal (162), dimethylamine, and trimethylamine.<sup>130</sup>



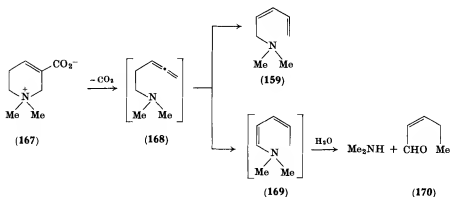
Formations of 6-dimethylamino-2,4-hexadiene (163) from 1,6-dimethyl-3-piperideine,<sup>87</sup> 5-dimethylamino-4-methyl-1,3-pentadiene (164) from 1,3-dimethyl-3-piperideine,<sup>82</sup> 5-dimethylamino-3-methyl-1,3-pentadiene (165) from 1,4-dimethyl-3-piperideine,<sup>83</sup> and 6-dimethylamino-2,4-heptadiene (166) from 1,2,6-trimethyl-3-piperideine<sup>94</sup> may serve as further examples of the Hofmann exhaustive methylation in the 3-piperideine series.



<sup>130</sup> R. Lukeš and J. Pliml, *Collect. Czech. Chem. Commun.* **21**, 625 (1956).



The thermal degradation of arecaidine methyl betaine (**167**) and the subsequent work-up with hydrochloric acid gave a mixture of 5-dimethylamino-1,3-pentadiene (**159**), *cis*-2-pentenal (**170**), and dimethylamine. The 1,2-diene (**168**) and the enamine (**169**) are assumed as the unisolated intermediates.<sup>131</sup>



## V. The Naturally Occurring 3-Piperidineines

### A. *Areca* ALKALOIDS

The 3-piperidineine nucleus is found in alkaloids of the *Areca* nut<sup>132–135</sup> (or betel nut, the fruit of *Areca catechu*, a palm tree of the far East), such as arecaidine (**167a**), arecoline (**168a**), guvacine (**169a**), and guvacoline (**170a**). Arecaidine is widely used in veterinary medicine.<sup>136</sup> Numerous syntheses of arecaidine<sup>137–141</sup> and arecoline<sup>141–151</sup> are known, the most simple consisting in the reduction of nicotinic

<sup>131</sup> M. Ferles, *Collect. Czech. Chem. Commun.* **29**, 2323 (1964).

<sup>132</sup> E. Jahns, *Ber.* **21**, 3404 (1888).

<sup>133</sup> E. Jahns, *Ber.* **23**, 2972 (1890).

<sup>134</sup> E. Jahns, *Ber.* **24**, 2615 (1891).

<sup>135</sup> K. Freudenberg, *Ber.* **51**, 1668 (1918).

<sup>136</sup> J. Blažek, *Českoslov. Farm.* **5**, 208 (1956); *Chem. Abstr.* **50**, 17333 (1956).

<sup>137</sup> A. Wohl and A. Johnson, *Ber.* **40**, 4712 (1907).

<sup>138</sup> A. Wohl and M. S. Losanitsch, *Ber.* **40**, 4723 (1907).

<sup>139</sup> N. A. Preobrazhenskii and L. B. Fisher, *Zh. Obshch. Khim.* **11**, 140 (1941); *Chem. Abstr.* **35**, 5505 (1941).

acid methiodide or methyl nicotinate methiodide with an alkali metal borohydride.<sup>150</sup> Many arecaidine derivatives modified on the carboxylic group,<sup>151-157</sup> as well as on the nitrogen atom,<sup>158-160</sup> have been reported.



(167a) R = Me, R' = H

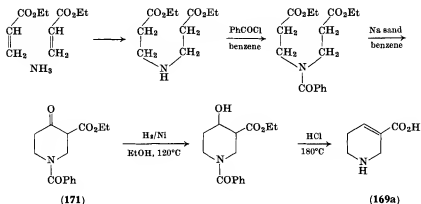
(168a) R = R' = Me

(169a) R = R' = H

(170a) R = H, R' = Me

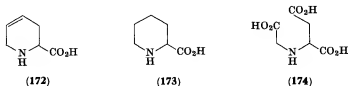
- <sup>140</sup> N. A. Preobrazhenskii, K. M. Malkov, M. E. Maurit, M. A. Vorob'ev, and A. S. Vlasov, *Zh. Obshch. Khim.* **27**, 3162 (1957); *Chem. Abstr.* **52**, 9162 (1958).
- <sup>141</sup> A. Dobrowsky, *Monatsh. Chem.* **83**, 443 (1952).
- <sup>142</sup> T. F. Dankova, E. A. Sidorova, and N. A. Preobrazhenskii, *Zh. Obshch. Khim.* **11**, 934 (1941); *Chem. Abstr.* **37**, 381 (1943).
- <sup>143</sup> P. S. Ugryumov, *Dokl. Akad. Nauk SSSR* **29**, 48 (1940); *Chem. Abstr.* **35**, 3644 (1941).
- <sup>144</sup> S. G. Tsarev, *Veterinariya* **29**, No. 11, 57 (1952); *Chem. Abstr.* **47**, 3981 (1953).
- <sup>145</sup> M. E. Maurit and N. A. Preobrazhenskii, *Zh. Obshch. Khim.* **28**, 968 (1958); *Chem. Abstr.* **52**, 17263 (1958).
- <sup>146</sup> C. Mannich, *Ber.* **75B**, 1480 (1942).
- <sup>147</sup> J. J. Panouse, *Compt. Rend.* **233**, 1200 (1951); *Chem. Abstr.* **46**, 6643 (1952).
- <sup>148</sup> J. Levy, U.S. Patent 2,569,182 (1951); *Chem. Abstr.* **46**, 5092 (1952).
- <sup>149</sup> L. H. Knox, U.S. Patent 2,506,458 (1950); *Chem. Abstr.* **45**, 671 (1951).
- <sup>150</sup> Nopco Chem. Comp., British Patent 646,220 (1950); *Chem. Abstr.* **45**, 2986 (1951).
- <sup>151</sup> Nopco Chem. Comp., Australian Patent 150,030 (1953); *Ref. Zh.* **1955**, 24886.
- <sup>152</sup> A. Wohl and M. S. Losanitsch, *Ber.* **40**, 4685 (1907).
- <sup>153</sup> A. Wohl, *Ber.* **38**, 4154 (1905).
- <sup>154</sup> V. Sapara, *Chem. Listy* **45**, 454 (1951); *Chem. Abstr.* **46**, 7570 (1952).
- <sup>155</sup> E. Merck and H. Maeder, German Patent 485,139 (1929).
- <sup>156</sup> V. Sapara, *Chem. Listy* **43**, 225 (1949); *Chem. Abstr.* **45**, 622 (1951).
- <sup>157</sup> A. Lasso and P. D. Waller, *J. Org. Chem.* **22**, 837 (1957).
- <sup>158</sup> S. M. McElvain and G. Stork, *J. Am. Chem. Soc.* **68**, 1049 (1946).
- <sup>159</sup> M. N. Shchukina, A. Ya. Berlin, and E. D. Sazonova, *Zh. Priklad. Khim.* **18**, 634 (1945); *Chem. Abstr.* **40**, 6471 (1946).
- <sup>160</sup> P. L. Kartsonis and J. A. Austin, U.S. Patent 2,557,353 (1951); *Chem. Abstr.* **45**, 8211 (1951).

In the synthesis of guvacine (**169a**), ethyl 1-benzoyl-4-piperidone-3-carboxylate (**171**) was used as the key intermediate.<sup>161</sup>



### B. BAIKIAIN

(-)-Baikiaia (**172**), (-)-4,5-dehydro-L-pipecolinic acid, was isolated from the African tree *Baikiaea plurijuga*.<sup>162</sup> Catalytic hydrogenation of **172** gave L-(-)-pipecolinic acid (**173**); *N*-carboxymethyl-L-aspartic acid (**174**) was obtained from **172** by ozonolysis.<sup>162</sup>



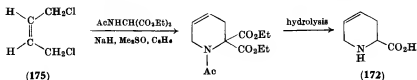
Racemic baikiaia can be obtained by an electrolytic reduction of picolinic acid<sup>60</sup> (see Section II, B, 2), by an eight-step synthesis from 1-benzoyloxy-4-bromo-2-butyne<sup>163</sup> or, more simply, from *cis*-1,4-dichloro-2-butene (**175**).<sup>164</sup>

<sup>161</sup> I. G. Farbenindustrie, Swiss Patent 175,168 (1935); *Chem. Zentr.* **1935**, II, 2699.

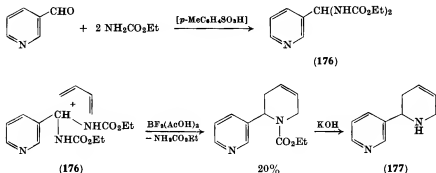
<sup>162</sup> F. E. King, T. J. King, and A. J. Warwick, *J. Chem. Soc.* 3590 (1950).

<sup>163</sup> N. A. Dobson and R. A. Raphael, *J. Chem. Soc.* 3642 (1958).

<sup>164</sup> A. W. Burgstahler and C. E. Aiman, *J. Org. Chem.* **25**, 489 (1960).

C. ANATABINE AND *N*-METHYLANATABINE

Anatabine (177) and *N*-methylanatabine are minor alkaloids of tobacco.<sup>165-167</sup> Racemic 177 was synthesized by the  $\text{BF}_3$ -catalyzed condensation (cf. Section II, A) of diethyl 3-pyridylmethylenebis-carbamate (176) with 1,3-butadiene and subsequent removal of the *N*-ethoxycarbonyl group.<sup>168, 169</sup>



## D. LOBININE AND ISOLOBININE

Lobinine<sup>170, 171</sup> (178) was obtained from residues after isolation of the main alkaloids of *Lobelia inflata* (lobinine was formerly proposed

<sup>165</sup> E. Späth and F. Keszler, *Ber.* **70**, 239 (1937).

<sup>166</sup> E. Späth and F. Keszler, *Ber.* **70**, 704 (1937).

<sup>167</sup> E. Späth and F. Keszler, *Ber.* **70**, 2450 (1937).

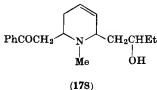
<sup>168</sup> P. M. Quan, T. K. B. Karns, and L. D. Quin, *Chem. Ind.* (London) 1553 (1964).

<sup>169</sup> P. M. Quan, T. K. B. Karns, and L. D. Quin, *J. Org. Chem.* **30**, 2769 (1965).

<sup>170</sup> H. Wieland and M. Ishimasa, *Ann.* **491**, 14 (1931).

<sup>171</sup> H. Wieland, W. Koschara, E. Dane, J. Renz, W. Schwarz, and W. Linde, *Ann.* **540**, 103 (1949).

as the structure of a hexamethyleneimine derivative<sup>170</sup>). Isolobinine seems to be a stereoisomer of lobinine.<sup>171, 172</sup>



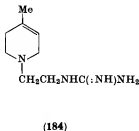
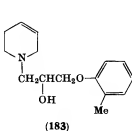
### E. OTHER 3-PIPERIDEINE DERIVATIVES

The structure of a 3-piperidine derivative was proposed tentatively for some further naturally occurring substances or their transformation products, e.g., pseudoconiceine<sup>173</sup> (179), tropidine<sup>174</sup> (180), and ecgonidine methyl ester<sup>175-177</sup> (181 or 182).

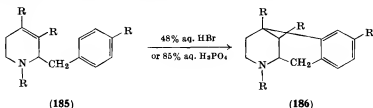


## VI. Pharmaceuticals Based on 3-Piperidine

1-(2-Hydroxy-3-*o*-tolylloxypropyl)-3-piperidine hydrochloride<sup>178</sup> (183) (Tolpronine) and 1-(2-guanidinoethyl)-4-methyl-3-piperidine hemisulfate<sup>179-182</sup> (184) (Lerone) may be given as representatives of physiologically active 3-piperidines.<sup>122, 183-186</sup>



Some 1-alkyl-2-benzyl-3-piperideines (**185**) were used in the Grewe synthesis of the benzomorphan-like analgesics (**186**). The ring closure between the ortho position of the benzyl residue and position 4 of the 3-piperideine nucleus was usually accomplished by heating in 48% hydrobromic acid or 85% phosphoric acid.<sup>41, 103, 188-193</sup>



## VII. Tabular Survey of Some Simple 3-Piperideines

Some simple 3-piperideines are listed in Table IV.

- <sup>172</sup> O. Thomä, *Ann.* **540**, 99 (1939).
- <sup>173</sup> E. Späth, F. Kuffner, and L. Ensfellner, *Ber.* **66**, 591 (1933).
- <sup>174</sup> R. Willstaetter, *Ber.* **34**, 129 (1901).
- <sup>175</sup> J. Matchett and J. Levine, *J. Am. Chem. Soc.* **63**, 2444 (1941).
- <sup>176</sup> S. P. Findlay, *J. Am. Chem. Soc.* **75**, 1033 (1953).
- <sup>177</sup> F. Zymalkovski, *Arch. Pharm.* **286**, 1 (1953).
- <sup>178</sup> Y. M. Beasley, V. Petrow, and O. Stephenson, *J. Pharm. Pharmacol.* **10**, 103 (1958); *Chem. Abstr.* **52**, 11836 (1958).
- <sup>179</sup> Farbenfabriken Bayer, German Patent 1,206,902 (1965).
- <sup>180</sup> Farbenfabriken Bayer, German Patent 1,211,208 (1966).
- <sup>181</sup> Farbenfabriken Bayer, British Patent 985,354 (1965); *Chem. Abstr.* **63**, 586 (1965).
- <sup>182</sup> G. Kroneberg, K. Schlossmann, and K. Stoepel, *Arzneimittel-Forsch.* **17**, 199 (1967).
- <sup>183</sup> J. T. Plati and W. Wenner, U.S. Patent 2,537,854 (1951); *Chem. Abstr.* **45**, 5192 (1951).
- <sup>184</sup> S. M. McElvain, W. B. Dickinson, and R. J. Athey, *J. Am. Chem. Soc.* **76**, 5625 (1954).
- <sup>185</sup> I. N. Nazarov, D. V. Sokolov, and G. S. Litvinenko, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 95 (1954); *Chem. Abstr.* **49**, 6250 (1955).
- <sup>186</sup> G. E. Bonvicino, U.S. Patent 3,072,648 (1963); *Chem. Abstr.* **58**, 13924 (1963).
- <sup>187</sup> N. B. Eddy, *Chem. Ind. (London)* 1462 (1959).
- <sup>188</sup> E. L. May and E. M. Fry, *J. Org. Chem.* **22**, 1366 (1957).
- <sup>189</sup> J. H. Ager and E. L. May, *J. Org. Chem.* **27**, 245 (1962).
- <sup>190</sup> J. H. Ager, S. E. Fullerton, and E. L. May, *J. Med. Chem.* **6**, 322 (1963).
- <sup>191</sup> S. E. Fullerton, J. H. Ager, and E. L. May, *J. Org. Chem.* **27**, 2554 (1962).
- <sup>192</sup> S. Saito and E. L. May, *J. Org. Chem.* **27**, 948 (1962).
- <sup>193</sup> N. B. Eddy, J. G. Murphy, and E. L. May, *J. Org. Chem.* **22**, 1370 (1957).

TABLE IV  
SIMPLE 3-PIPERIDEINES

Formula	3-Piperidine	Preparative method <sup>a</sup>	Boiling point (°C)	Salt <sup>b</sup> melting point (°C)
C <sub>5</sub> H <sub>9</sub> N	Unsubstituted	<i>A</i> , <sup>76</sup> <i>B</i> , <sup>47</sup> <i>G</i> , <sup>1, 52, 128</sup>	113.5 <sup>128</sup>	<i>a</i> <sup>47</sup> 160–162 <i>b</i> <sup>47</sup> 200–201
C <sub>6</sub> H <sub>11</sub> N	1-Methyl-	<i>D</i> , <sup>100</sup> <i>F</i> <sup>81</sup>	112.5 <sup>81</sup>	<i>a</i> <sup>100</sup> 201 <i>b</i> <sup>100</sup> 191
	3-Methyl-	<i>A</i> , <sup>76</sup> <i>B</i> , <sup>47</sup> <i>C</i> , <sup>47</sup> <i>E</i> <sup>76</sup>	140–141 <sup>98</sup>	<i>a</i> <sup>47</sup> 161 <i>b</i> <sup>47</sup> 170
	4-Methyl-	<i>A</i> , <sup>76</sup> <i>B</i> , <sup>76</sup> <i>C</i> , <sup>47</sup> <i>G</i> <sup>58</sup>	135–136 <sup>47</sup>	<i>a</i> <sup>47</sup> 146 <i>b</i> <sup>47</sup> 171
	6-Methyl-	<i>A</i> , <sup>76</sup> <i>B</i> , <sup>47</sup> <i>G</i> <sup>58</sup>	125 <sup>58</sup>	<i>a</i> <sup>60</sup> 227 <i>b</i> <sup>47</sup> 202–203
C <sub>7</sub> H <sub>13</sub> N	1,2-Dimethyl-	<i>G</i> <sup>65</sup>	127 <sup>65</sup>	<i>a</i> <sup>65</sup> 217
	1,3-Dimethyl-	<i>B</i> , <sup>64</sup> <i>D</i> , <sup>100</sup> <i>E</i> <sup>64</sup>	137–138 <sup>61</sup>	<i>a</i> <sup>100</sup> 105 <i>b</i> <sup>64</sup> 177.5
	1,4-Dimethyl-	<i>B</i> , <sup>100</sup> <i>D</i> , <sup>100</sup> <i>E</i> , <sup>64</sup> <i>F</i> <sup>83</sup>	135–136 <sup>83</sup>	<i>a</i> <sup>100</sup> 146 <i>b</i> <sup>83</sup> 175
	1,5-Dimethyl-	<i>G</i> <sup>66</sup>	126.5 <sup>66</sup>	<i>a</i> <sup>66</sup> 135–136
	1,6-Dimethyl-	<i>B</i> , <sup>64</sup> <i>D</i> <sup>100</sup>	132–132.5 <sup>87</sup>	<i>a</i> <sup>60</sup> 226 <i>b</i> <sup>100</sup> 196
	2,6-Dimethyl-	<i>B</i> <sup>47</sup>	132 <sup>61</sup>	<i>b</i> <sup>47</sup> 212
	3,4-Dimethyl-	<i>A</i> , <sup>61</sup> <i>B</i> <sup>61</sup>	138 <sup>61</sup>	—
	3,5-Dimethyl-	<i>A</i> , <sup>61</sup> <i>B</i> , <sup>61</sup> <i>C</i> <sup>61</sup>	141 <sup>61</sup>	—
	4,6-Dimethyl-	<i>B</i> <sup>63</sup>	145–148 <sup>63</sup>	<i>b</i> <sup>63</sup> 167
	1-Ethyl-	<i>D</i> <sup>102</sup>	135–136 <sup>102</sup>	<i>a</i> <sup>102</sup> 171–172 <i>b</i> <sup>102</sup> 170–171
	3-Ethyl-	<i>B</i> <sup>48</sup>	142 <sup>48</sup>	<i>b</i> <sup>48</sup> 194
	4-Ethyl-	<i>A</i> , <sup>48</sup> <i>B</i> , <sup>48</sup> <i>C</i> <sup>48</sup>	160 <sup>48</sup>	<i>b</i> <sup>48</sup> 160
	5-Ethyl-	<i>B</i> <sup>48</sup>	158 <sup>48</sup>	<i>b</i> <sup>48</sup> 164

C <sub>8</sub> H <sub>15</sub> N	1,2,3-Trimethyl-	A <sup>77</sup>	154 <sup>77</sup>	—
	1,2,4-Trimethyl-	G <sup>65</sup>	149 <sup>65</sup>	a <sup>65</sup> 179
	1,2,5-Trimethyl-	A, <sup>77</sup> B <sup>77</sup>	150 <sup>77</sup>	—
	1,3,4-Trimethyl-	A, <sup>77</sup> B <sup>77</sup>	154-156 <sup>77</sup>	—
	1,3,5-Trimethyl-	A, <sup>77</sup> B <sup>77</sup>	149 <sup>77</sup>	—
	1,4,5-Trimethyl-	A, <sup>77</sup> B <sup>77</sup>	148 <sup>77</sup>	—
	1,4,6-Trimethyl-	B <sup>65</sup>	155 <sup>65</sup>	a <sup>65</sup> 184-185 b <sup>65</sup> 154
	<i>cis</i> -2,4,6-Trimethyl-	C <sup>54</sup>	149 <sup>54</sup>	—
	1-Methyl-3-ethyl-	D <sup>102</sup>	159.5-161 <sup>102</sup>	a <sup>102</sup> 119-120.5 b <sup>102</sup> 178-180
	1-Methyl-4-ethyl-	D <sup>102</sup>	158-160 <sup>102</sup>	—
	3-Methyl-4-ethyl-	A, <sup>48</sup> B <sup>61</sup>	183-185 <sup>48</sup>	b <sup>48</sup> 117-118
	1-Ethyl-3-methyl-	D <sup>102</sup>	157 <sup>102</sup>	a <sup>102</sup> 105.5-106.5 b <sup>102</sup> 178-180
	1-Ethyl-4-methyl-	D <sup>102</sup>	157.5-158 <sup>102</sup>	a <sup>102</sup> 157-158
	1-Ethyl-6-methyl-	D <sup>102</sup>	150-151 <sup>102</sup>	a <sup>102</sup> 182-183
	3-Ethyl-6-methyl-	A, <sup>48</sup> B, <sup>48</sup> C <sup>48</sup>	170-171 <sup>48</sup>	b <sup>48</sup> 179
	4-Ethyl-3-methyl-	A, <sup>61</sup> B, <sup>61</sup> C <sup>61</sup>	171 <sup>61</sup>	—
	4-Propyl-	C <sup>45</sup>	178-179.5 <sup>45</sup>	—
	4-Isopropyl-	B, <sup>58</sup> G <sup>48</sup>	174-176 <sup>48</sup>	a <sup>58</sup> 169.5-171 b <sup>58</sup> 139.5
	5-Isopropyl-	B <sup>48</sup>	174-176 <sup>48</sup>	b <sup>48</sup> 201
C <sub>9</sub> H <sub>17</sub> N	<i>cis</i> -1,2,4,6-Tetramethyl-	B <sup>54</sup>	159 <sup>54</sup>	—
	1,2-Dimethyl-5-ethyl-	A <sup>61</sup>	165 <sup>61</sup>	—
	1,3-Dimethyl-4-ethyl-	A, <sup>102</sup> B, <sup>102</sup> D <sup>102</sup>	178-179.5 <sup>102</sup>	b <sup>102</sup> 129-130
	1,6-Dimethyl-3-ethyl-	A, <sup>77</sup> D <sup>102</sup>	178-179 <sup>102</sup>	b <sup>102</sup> 192
	4-Butyl-	C <sup>45</sup>	196-197 <sup>45</sup>	—
C <sub>11</sub> H <sub>13</sub> N	1-Phenyl-	F <sup>84</sup>	45.5-46.5 <sup>84</sup> (m.p.)	a <sup>84</sup> 146-147

<sup>a</sup> Methods: A, AlH<sub>3</sub> reduction; B, electrolytic reduction; C, Ladenburg reduction; D, NaBH<sub>4</sub> reduction; E, LiAlH<sub>4</sub> reduction; F, Formic acid reduction; and G, other methods.

<sup>b</sup> Salts: a, picrate and b, hydrobromide of a dibromide.



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# Advances in Imidazole Chemistry

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## I. Introduction

A comprehensive monograph on imidazole and its derivatives by K. Hofmann<sup>1</sup> was published in 1953. A chapter dealing with imidazoles and condensed imidazoles by Schipper and Day<sup>2</sup> in "Heterocyclic Compounds" edited by Elderfield reviewed the literature to 1955, while a more recent review by Pozharskii *et al.*<sup>3</sup> brought the chemistry of imidazole and some important condensed imidazoles up to date to 1964. A number of monographs on the chemistry of heterocyclic compounds<sup>4-10</sup> have also dealt with aspects of imidazole chemistry in a necessarily brief manner. Specific topics in imidazole chemistry and biochemistry have been covered in further reviews.<sup>11-21</sup> In the most

<sup>1</sup> K. Hofmann, in "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), Imidazole and Derivatives, Part 1. Interscience, New York, 1953.

<sup>2</sup> E. S. Schipper and A. R. Day, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 5, p. 194. Wiley, New York, 1957.

<sup>3</sup> A. F. Pozharskii, A. D. Garnovskii, and A. M. Simonov, *Usp. Khim.* **35**, 261 (1966); *Russ. Chem. Rev.*, **35**, 122 (1966).

<sup>4</sup> J. D. Loudon, in "Chemistry of Carbon Compounds" (E. H. Rodd, ed.), Vol. 4A, p. 286. Elsevier, Amsterdam, 1957.

<sup>5</sup> A. Albert, "Heterocyclic Chemistry." Athlone Press, London, 1959.

<sup>6</sup> R. Acheson, "Introduction to the Chemistry of Heterocyclic Compounds," 2nd ed. Wiley, New York, 1967.

<sup>7</sup> F. Möller, in "Methoden der organischen Chemie" (Houben-Weyl, ed.), Vol. 11, Part 1, p. 9. Thieme, Stuttgart, 1957.

<sup>8</sup> M. H. Palmer, "The Structure and Reactions of Heterocyclic Compounds." Edward Arnold, London, 1967.

<sup>9</sup> A. R. Katritzky and J. M. Lagowski, "The Principles of Heterocyclic Chemistry." Methuen, London, 1967.

<sup>10</sup> J. Ridd, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. 1, p. 109. Academic Press, New York, 1963.

<sup>11</sup> K. Takemoto, *Kagaku (Kyoto)* **23**, 436, 518 (1968); *Chem. Abstr.* **69**, 96515, 96518 (1968).

<sup>12</sup> H. A. Staab and W. Rohr, in "Newer Methods of Preparative Organic Chemistry" (W. Foerst, ed.), Vol. 5, p. 61. Academic Press, New York, 1968.

<sup>13</sup> E. A. Barnard and W. D. Stein, *Advan. Enzymol.* **20**, 51 (1958).

<sup>14</sup> J. Wright, *Chem. Rev.* **48**, 397 (1951).

<sup>15</sup> A. R. Day, *Trans. N.Y. Acad. Sci.* **20**, 3 (1957).

<sup>16</sup> S. E. Severin, *Usp. Sovrem. Biol.* **59**, 165 (1965); *Chem. Abstr.* **63**, 6177 (1965).

<sup>17</sup> M. R. Grimmett, *Rev. Pure Appl. Chem.* **15**, 101 (1965).

<sup>18</sup> I. Jezo, *Listy Cukrovar.* **82**, 259 (1966); *Chem. Abstr.*, **67**, 3201 (1967).

recent of these, Takemoto<sup>11</sup> has discussed hydrogen bonding, metal complexes, and catalytic activity, while Staab and Rohr<sup>12</sup> have made an extensive coverage of the reactive and synthetically important imidazolides. In the present article the aim is to review developments in imidazole chemistry as far as possible to the end of 1968. It is proposed to discuss methods of synthesis and reactions only of the simple imidazole ring. Accordingly, little reference will be made to condensed imidazoles (such as benzimidazole, purines, etc.), or to compounds containing reduced imidazole rings. No attempt has been made to review the now extensive literature dealing with the pharmacology, biology, and metal complexes of imidazoles, nor is there any attempt to survey the studies of imidazole-catalyzed hydrolysis of esters in biological systems.

In the section dealing with the synthesis of the imidazole ring (Section II) the system used by Katritzky<sup>9</sup> and Loudon<sup>4</sup> has been adopted, listing syntheses under the headings of specific bond formation. Although this method may involve some minor classification difficulties it has, in the author's opinion, the advantages of focusing attention on the similarities of many synthetic procedures, and permits ready evaluation of the most likely methods for obtaining suitably substituted products.

In order to achieve some degree of completeness, references to selected papers and articles published before 1963 have been included, while, in the light of more recent work, aspects dealt with in the earlier review of Pozharskii *et al.*<sup>3</sup> are discussed again.

## II. Syntheses of the Imidazole Ring System

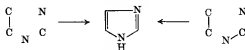
It becomes apparent when one is faced with a synthetic problem in imidazole chemistry that there is no single, widely applicable synthetic procedure. Even the methods devised by Bredereck (Section II, A) and the reaction of  $\alpha$ -aminoketones with cyanates or thiocyanates (Section II, F) have limitations.

<sup>11</sup> L. B. Townsend, *Chem. Rev.* **67**, 533 (1967).

<sup>12</sup> S. E. Severin, *Usp. Sovrem. Biol.* **64**, 181 (1967); *Chem. Abstr.* **68**, 26857 (1968).

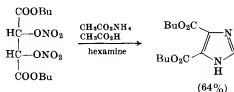
<sup>21</sup> D. B. Melville, *Vitamins Hormones* **17**, 156 (1959).

### A. FORMATION OF THE 1:5-, 2:3-, 3:4- (AND SOMETIMES ALSO THE 1:2-) BONDS



SCHEME 1

Reactions of this type include the major early methods used by Debus,<sup>22</sup> Radziszewski,<sup>23</sup> Weidenhagen,<sup>24</sup> and Maquenne.<sup>25</sup> All these suffer from deficiencies such as difficulty of synthesis of starting materials, low yields, and, more often than not, from the formation of mixtures of products which require tedious separation. Among recent modifications<sup>26,27</sup> of the Maquenne method is the preparation of dialkyl 4,5-imidazole dicarboxylates in yields of 45–65% by treatment of a dialkyltartrate dinitrate with either an aliphatic aldehyde or a formaldehyde precursor, in the presence of ammonium ions at pH 3.5–6.5.



Hydrolysis (especially with bromoacetic acid)<sup>28</sup> of the dicarboxylic esters can be followed by decarboxylation and it is possible to remove one carboxyl group at a time to prepare the imidazole-4-carboxylic acid. The decarboxylation of imidazolecarboxylic acids has been discussed by Schipper and Day.<sup>2</sup>

<sup>22</sup> H. Debus, *Ann.* **107**, 204 (1858).

<sup>23</sup> B. Radziszewski, *Ber.* **15**, 2706 (1882).

<sup>24</sup> R. Weidenhagen and R. Herrmann, *Ber.* **68**, 1953 (1935).

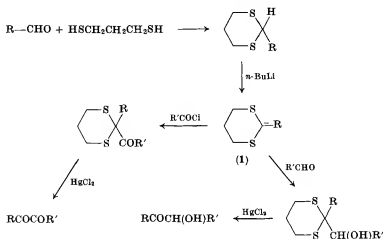
<sup>25</sup> M. Maquenne, *Ann. Chim. Phys.* **24**, 525 (1891).

<sup>26</sup> W. J. Palaveda and E. F. Schoenewaldt, *U.S. Patent* 2,905,692; *Chem. Abstr.* **54**, 14272 (1960).

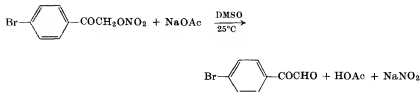
<sup>27</sup> H. Schubert and H. Ladish, *J. Prakt. Chem.* **18**, 199 (1962); *Chem. Abstr.* **58**, 4542 (1963).

<sup>28</sup> P. M. Kochergin, *Zh. Obshch. Khim.* **31**, 184 (1961); *Chem. Abstr.* **55**, 22293 (1961).

The  $\alpha$ -dicarbonyl compounds required as starting materials in the Radziszewski synthesis are often difficult to prepare. A recent method of synthesis of such compounds has been described<sup>29</sup> using propane-1,3-dithiol to prepare a stable dithiane anion (1), which can be converted into either an  $\alpha$ -diketone or an  $\alpha$ -hydroxyketone.



A further efficient synthesis of glyoxals and  $\alpha$ -diketones involves the reaction of an  $\alpha$ -ketonitrate ester with sodium acetate in dimethyl



sulfoxide (DMSO).<sup>30</sup> Aryl  $\alpha$ -diketones are available from  $\alpha$ -diketanils which are prepared by a cyanide ion-catalyzed transformation of aromatic aldimines.<sup>31</sup>

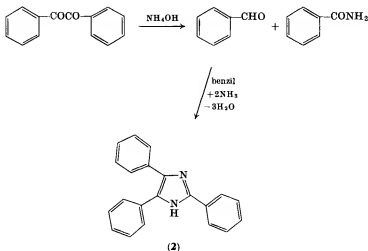
One of the first imidazole derivatives prepared by the action of ammonia on an  $\alpha$ -diketone was lophine (2,4,5-triphenylimidazole,

<sup>29</sup> E. J. Corey and D. Seebach, *Angew. Chem., Intern. Ed. Engl.* **4**, 1075 (1965).

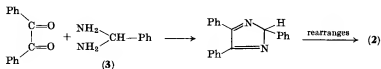
<sup>30</sup> N. Kornblum and H. W. Frazier, *J. Am. Chem. Soc.* **88**, 865 (1966).

<sup>31</sup> J. S. Walia, J. Singh, M. S. Chattha, and M. Satyanarayana, *Tetrahedron Letters* 195 (1969).

2).<sup>32</sup> For this reaction between benzil and ammonia, Davidson *et al.*<sup>33</sup> suggested a mechanism which did not involve fission of the bond between the carbonyl groups to yield benzaldehyde. Although this mechanism (which has been discussed in a previous review<sup>1</sup>) was able to account satisfactorily for the reaction products and intermediates which were isolated, more recent studies would suggest that cleavage occurs between the carbonyl functions yielding a molecule of benzaldehyde and a molecule of benzamide. The observation that addition of



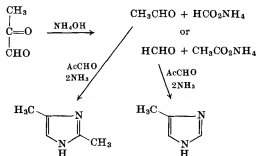
excess hexamethylenetetramine to benzil and ammonium acetate results in the formation mainly of 4,5-diphenylimidazole and the fact that lophine can also be formed by the interaction of benzil, ammonia, and benzaldehyde was explained by Davidson *et al.*<sup>33</sup> by postulating a diamine intermediate (3) from the aldehyde. This suggestion fails to



<sup>32</sup> N. Zinin, *Ann.* **34**, 186 (1840).

<sup>33</sup> D. Davidson, M. Weiss, and M. Jelling, *J. Org. Chem.* **2**, 319 (1937).

account for the observation of Grimmett and Richards<sup>34</sup> that equimolecular proportions of 4-methylimidazole<sup>34a</sup> and 2,4-dimethylimidazole are formed when pyruvaldehyde reacts with concentrated aqueous ammonia. It seems possible that the  $\alpha$ -dicarbonyl compound in this case might be reacting with the ammonia solution by two routes at about equal rates. Support for this reaction pathway is pro-



vided by the isolation of acetamide on sublimation of a pyruvaldehyde-ammonia reaction mixture,<sup>35</sup> and by the isolation of propionamide from an ammoniacal solution of 1-hydroxybutan-2-one acetate.<sup>35</sup> The evidence available at present does not adequately distinguish between the mechanisms for the reaction of an  $\alpha$ -dicarbonyl compound with ammonia, and it may be that both pathways contribute to the reaction products.

Recent applications of this synthetic procedure include syntheses of 2,4,5-triarylimidazoles<sup>36</sup> and the reaction of acenaphthoquinone with benzaldehyde in the presence of ammonia.<sup>37</sup> An elegant synthesis of 4,5-di-*tert*-butylimidazole (4)<sup>38</sup> proceeds through reaction of an  $\alpha$ -diketone with formaldehyde and ammonia. Formamide often proves a convenient substitute for ammonia. For example, the reaction of an

<sup>34</sup> M. R. Grimmett and E. L. Richards, *J. Chem. Soc.* 3751 (1965).

<sup>34a</sup> Throughout the text (except in discussions relating to the tautomerism of imidazoles) substitution in the 4 (or 5)-positions of *N*-unsubstituted imidazoles will be referred to as 4-substitution.

<sup>35</sup> M. R. Grimmett, unpublished material.

<sup>36</sup> T. E. MacDermott, *Australian J. Chem.* 19, 2181 (1966).

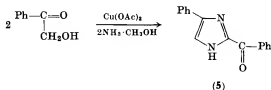
<sup>37</sup> O. Tsuge and T. Gunjima, *Asahi Garasu Gijutsu Shorei-Kai Kenkyu Hokoku* 12, 209 (1966); *Chem. Abstr.* 68, 78248 (1966).

<sup>38</sup> H. Wynberg and A. d. Groot, *Chem. Commun.* 171 (1965).

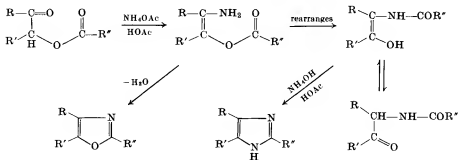




methanolic ammoniacal cupric acetate yields 32% 2-benzoyl-4-phenylimidazole (5).<sup>41</sup> Similar methods were employed by Huebner<sup>42</sup>



to prepare histamine analogs and by Mackay and Shepherd<sup>43</sup> for the synthesis of potential histidine decarboxylase inhibitors. Even in the absence of cupric salts, acyloins are still capable of forming imidazoles with ammonia. Thus, in aqueous ammonia, 1,4-dihydroxybutan-2-one forms 4-(2'-hydroxyethyl)imidazole<sup>35</sup> and 1-hydroxybutan-2-one acetate forms 4-ethylimidazole (and other products) in low yield.<sup>35</sup> The reaction of  $\alpha$ -acyloxyketones with ammonium acetate<sup>44</sup> results in the formation of mixtures of oxazoles and imidazoles.



Cheap sources of acyloins are the reducing carbohydrates, and a number of new imidazoles have been isolated from the reaction of ammonia with these compounds. From the interaction of D-glucose and aqueous ammonia, Komoto has obtained 2-hydroxymethyl-4-methylimidazole,<sup>45</sup> 4-(2'-hydroxyethyl)imidazole,<sup>38</sup> 4-(2',3'-dihydro-

<sup>41</sup> H. Schubert, *J. Prakt. Chem.*, **8**, 333 (1959); *Chem. Abstr.*, **55**, 4487 (1961).

<sup>42</sup> C. F. Huebner, U.S. Patent 2, 744, 899 (1956); *Chem. Abstr.* **51**, 487 (1957).

<sup>43</sup> D. Mackay and D. M. Shepherd, *Brit. J. Pharmacol.* **15**, 552 (1960).

<sup>44</sup> P. P. E. Strzbný, T. van Es, and O. G. Backeberg, *J. Org. Chem.*, **28**, 3381 (1963).

<sup>45</sup> M. Komoto, *J. Agr. Chem. Soc. Japan* **36**, 407, 461 (1962).

xypopyl)imidazole,<sup>45,46</sup> and 4-(2',3',4'-trihydroxybutyl)imidazole.<sup>45</sup> From rhamnose and ammonia the same worker isolated 4-ethylimidazole and 4-(2',3'-dihydroxybutyl)imidazole.<sup>47</sup> Dudkin<sup>48</sup> claims to have isolated imidazole, along with the expected 4-methyl- and 4-hydroxymethylimidazole, from the reaction of D-glucose with ammonia vapor. From the reactions of lactose, cellobiose, sucrose, and a number of starches with ammonia at high temperature and pressure (conditions under which alkaline hydrolysis of sucrose might be expected to be relatively extensive), Jezo<sup>49,50</sup> isolated a number of simple imidazoles, along with some pyrazines. At the temperatures employed, any polyhydroxyalkyl side chains were presumably extensively degraded. When glycinamide was substituted for ammonia, it still proved possible to identify imidazoles.<sup>51</sup> Imidazolines have been prepared from 2-amino-2-deoxyhexoses.<sup>52</sup> Imidazoles similar to those obtained by Komoto from glucose have been isolated from the action of ammonium hydroxide on glyceraldehyde,<sup>53</sup> pyruvaldehyde,<sup>54</sup> glycolaldehyde,<sup>54</sup> hydroxypyruvaldehyde,<sup>54</sup> and 3-O-methyl-D-glucose.<sup>55</sup> Carbohydrate sources have been used for the synthesis of 4-hydroxymethylimidazole<sup>56,57</sup> and 4-methylimidazole.<sup>58</sup> Even the reaction of wood<sup>59</sup> with ammonia

<sup>46</sup> S. Fujii, H. Tsuchida, and M. Komoto, *Agr. Biol. Chem. (Tokyo)* **30**, 73 (1966).

<sup>47</sup> H. Tsuchida and M. Komoto, *Agr. Biol. Chem. (Tokyo)* **31**, 185 (1967); **32**, 983 (1968).

<sup>48</sup> M. S. Dudkin, N. G. Shkantova, and A. F. Yatsuk, *Zh. Prikl. Khim.* **41**, 385 (1968).

<sup>49</sup> I. Jezo, *Chem. Zvesti* **17**, 126 (1963); *Chem. Abstr.* **60**, 4139 (1964); I. Jezo and I. Luzac, *Chem. Zvesti* **17**, 255, 865 (1963); **20**, 586 (1966); *Chem. Abstr.* **60**, 4139 (1964), **61**, 2039 (1964); **65**, 18669 (1966).

<sup>50</sup> I. Jezo, *Listy Cukrovar.* **82**, 300 (1966); *Chem. Abstr.* **66**, 66989 (1967).

<sup>51</sup> I. Jezo and I. Luzac, *Chem. Zvesti* **22**, 190 (1968).

<sup>52</sup> H. Fritz, C. J. Morel, and O. Wachter, *Helv. Chim. Acta* **51**, 569 (1968).

<sup>53</sup> M. R. Grimmett and E. L. Richards, *Australian J. Chem.* **17**, 1379 (1964).

<sup>54</sup> M. R. Grimmett and E. L. Richards, *Australian J. Chem.* **18**, 1855 (1965).

<sup>55</sup> M. R. Grimmett, R. Hodges, and E. L. Richards, *Australian J. Chem.* **21**, 505 (1968).

<sup>56</sup> R. J. Meltzer, A. Lewis, F. McMillan, J. Genzer, F. Leonard, and J. King, *J. Am. Pharm. Assoc.* **42**, 594 (1953); *Chem. Abstr.* **49**, 1018 (1955).

<sup>57</sup> A. E. Onis'chuk and O. K. Nikiforova, *Zh. Prikl. Khim.* **29**, 789 (1956); *Chem. Abstr.* **50**, 15515 (1956).

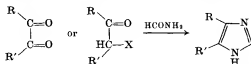
<sup>58</sup> R. W. Liggett and H. L. Hoffman, U.S. Patent 3,030,376 (1962); *Chem. Abstr.* **57**, 9859 (1962).

<sup>59</sup> Y. Okiwara and Y. Okiwara, *Kami-pa Gikyashi* **20**, 89 (1966); *Chem. Abstr.* **64**, 19959 (1966).

has produced 4-methylimidazole. Generally, however, the mixtures of products obtained, and the low yields, make carbohydrates an unsatisfactory source of imidazoles. An examination of the imidazoles formed in the reaction between hexose disaccharides and ammonia has led to the development of a method of linkage identification in the sugars.<sup>60</sup> The field of carbohydrate-ammonia reactions has been reviewed.<sup>17</sup>

Perhaps the most valuable advance in the field of imidazole synthesis has come from the method developed by Brederick and Theilig.<sup>61</sup> Their "formamide synthesis" of imidazoles involves the interaction of  $\alpha$ -diketones,  $\alpha$ -hydroxy-,  $\alpha$ -halogeno- or  $\alpha$ -aminoketones,  $\alpha$ -ketol esters, or (under reducing conditions)  $\alpha$ -oximinoketones, with formamide, and usually results in high yields (40–90%). Schubert<sup>62, 63</sup> has used the method to prepare a number of substituted imidazoles, e.g., 4,5-nonamethylene- and 4,5-undecamethyleneimidazole from the corresponding cycloalkanones with formamide.<sup>63</sup>

Although reviews dealing with general syntheses involving formamide have appeared<sup>64, 65</sup> a summary of the work pertaining to imidazole synthesis would appear to be desirable at this stage. The general reaction can be formulated as in the following reaction scheme, where



X = halogen, OH, NH<sub>2</sub>, or -OCOR". As the applicability of this method to the synthesis of 2-substituted imidazoles depends on the use of amides other than formamide, limitations have been imposed on the procedure, although various 2-methylimidazoles have been prepared using acetamide.<sup>66</sup>

<sup>60</sup> M. R. Grimmett, R. W. Bailey, and E. L. Richards, *Chem. Ind. (London)* 651 (1965).

<sup>61</sup> H. Brederick and G. Theilig, *Ber.* **86**, 88 (1953).

<sup>62</sup> H. Schubert, *J. Prakt. Chem.* **3**, 146 (1956); *Chem. Abstr.* **54**, 7694 (1960).

<sup>63</sup> H. Schubert and R. Schwaiberger, *Z. Chem.* **7**, 461 (1967); *Chem. Abstr.* **68**, 49508 (1968).

<sup>64</sup> H. Brederick, R. Gompper, H. G. Schuh, and G. Theilig, *Angew. Chem.* **71**, 753 (1959).

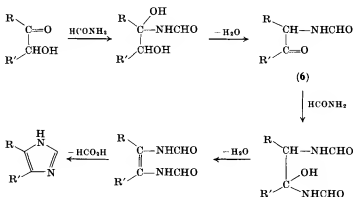
<sup>65</sup> H. Brederick, R. Gompper, H. G. Schuh, and G. Theilig, in "Newer Methods of Preparative Organic Chemistry" (W. Foerst, ed.), Vol. 3, p. 241. Academic Press, New York, 1964.

<sup>66</sup> F. Marquez, *Anales Real Soc. Espan. Fis. Quim. (Madrid) Ser. B* **57**, 723 (1961); *Chem. Abstr.* **57**, 12467 (1962).

The formation of oxazoles may begin to predominate if conditions in which the imidazole ring is formed preferentially (large excess of formamide at 180°–200°C, or passage of a stream of ammonia at 150°–175°C for 4–6 hours)<sup>66</sup> are not maintained. This situation is also favored by the use of sulfuric acid as the condensing medium.<sup>67</sup>

Perhaps the simplest method of imidazole synthesis involves bromination of a ketone in the presence of formamide<sup>68</sup> (or acetamide<sup>66</sup>). Where unsymmetrical ketones are involved it should prove possible to orientate selectively the bromine atom on either side of the carbonyl function by careful control of the solvent,<sup>69</sup> although no study of this facet appears to have been made.

Imidazole, itself, is prepared in 60% yield from the reaction of bromoacetaldehyde (as the glycol acetal), formamide, and ammonia at 180°C.<sup>70</sup> The initial step in the formation of imidazoles from  $\alpha$ -haloketones is replacement of the halogen by an hydroxy group.<sup>65</sup> From the stage of acyloin formation it is assumed<sup>61</sup> that the following reaction path is followed:



Evidence for this reaction pathway came from the observations that the  $\alpha$ -formamidoketone (6) could be isolated, and reaction with formamide converted it into the imidazole.<sup>67</sup> Although, in theory, it is

<sup>67</sup> H. Brederick and R. Gompper, *Ber.* **87**, 700, 726 (1954).

<sup>68</sup> H. Brederick, F. Effenberger, F. Marquez, and K. Ockewitz, *Ber.* **93**, 2083 (1960).

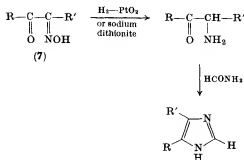
<sup>69</sup> M. Gaudry and A. Marquet, *Bull. Soc. Chim. France* 1849 (1967).

<sup>70</sup> H. Brederick, R. Gompper, R. Baugert and H. Herlinger, *Angew. Chem.* **70**, 269 (1958); *Ber.* **97**, 827 (1964).

possible that the  $\alpha$ -formamidoketone might form an imidazole via an oxazole this alternative may be excluded since  $\alpha$ -formamidoketones give oxazoles only to a minor extent if heated in the absence of a condensing agent, and oxazoles are not converted into imidazoles at temperatures as low as 150°C.<sup>71</sup>

In the reaction of  $\alpha$ -diketones with formamide and formaldehyde at 180°–200°C, no  $\alpha$ -hydroxyketones can be detected during the reaction,<sup>65</sup> and hence formaldehyde cannot be acting as a reducing agent. It seems then that imidazole formation must be due to generation of ammonia from formamide and subsequent reaction between the diketone, ammonia, and formaldehyde. The advantage of this method over the older Radziszewski synthesis lies in the reduced decomposition of the diketone with consequent reduction in side reactions which normally produce mixtures of imidazoles.

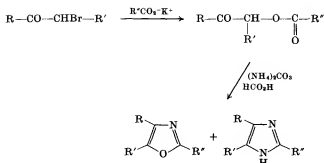
$\alpha$ -Aminoketones readily form imidazoles with formamide,<sup>61</sup> but, as the  $\alpha$ -aminoketones are often difficult to prepare, they can be replaced by their precursors, the corresponding isonitrosoketones (7), which are reduced with dithionite (or catalytically) in formamide at 70°–100°C. The ring is closed at higher temperatures.<sup>61</sup>



The use of  $\alpha$ -ketol esters with formamide has been reported by Novelli and de Santis<sup>72</sup> for the synthesis of oxazoles and imidazoles. It appears that in this case the reaction proceeds through reaction of the oxazole with formamide. The  $\alpha$ -ketol esters are prepared by treating the corresponding  $\alpha$ -bromoketones with the potassium salt of the appropriate carboxylic acid.

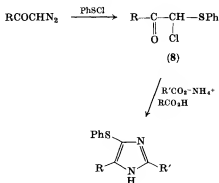
<sup>71</sup> G. Theilig, *Ber.* **86**, 96 (1953).

<sup>72</sup> A. Novelli and A. de Santis, *Tetrahedron Letters* **265** (1967).



Reaction of 1-chloro-1,2-epoxides with formamide yields 4,5-disubstituted imidazoles.<sup>73</sup>

A further reaction which appears to involve the formation of 1:5-, 2:3-, and 3:4-bonds is the reaction of  $\alpha$ -chloro- $\alpha$ -phenylmercapto-ketones (8) (prepared from the corresponding  $\alpha$ -diazoketones) with liquid carboxylic acids and ammonia.<sup>74</sup> The course of the reaction is not clearly understood, but shows similarities to the reaction of

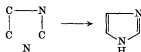


$\alpha$ -haloketones with amides. The method has been used<sup>74</sup> to prepare 2-ethyl-4-methyl-5-phenylthioimidazole in 32% yield from ammonia, propionic acid, and  $\alpha$ -chloro- $\alpha$ -phenylthioiketone.

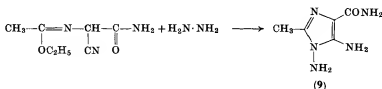
<sup>73</sup> A. A. Durgaryan, *Izv. Akad. Nauk. Armyan. SSR, Khim. Nauki* **15**, 481 (1962); *Chem. Abstr.* **58**, 13935 (1963).

<sup>74</sup> H. J. Bestmann and E. Singer, in "Newer Methods of Preparative Organic Chemistry" (W. Foerst, ed.), Vol. 3, p. 487. Academic Press, New York, 1964.

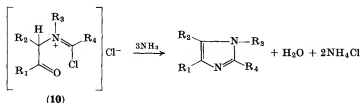
## B. FORMATION OF THE 1:2- AND 1:5-BONDS



Ethyl *N*-cyanomethylacetimidate (or formimidate) reacts with primary amines to form 1-substituted 5-aminoimidazoles.<sup>75, 76</sup> Similarly, reaction between ethyl *N*-(carbamoylcyanomethyl)formimidate (and other imidates) and hydrazine, phenylhydrazine, or 2-methylsemicarbazide yields 1-aminoimidazole-4-carboxyamides



(9).<sup>77</sup> The reaction has been adequately discussed by Pozharskii.<sup>3</sup> Recently, 1,2,4,5-tetraarylimidazoles and 1,2,3,4,5-pentaarylimidazolium salts have been prepared<sup>78</sup> from [*N*-( $\alpha$ -chloroaryliden)anilino]-deoxybenzoin chlorides (10) with ammonia or an aromatic primary amine, followed in the latter case by reaction with thionyl chloride.



<sup>75</sup> G. Shaw, R. N. Warrener, D. N. Butler, and R. K. Ralph, *J. Chem. Soc.* 1648 (1959).

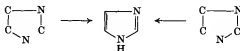
<sup>76</sup> G. Shaw and D. V. Wilson, *J. Chem. Soc.* 2937 (1962).

<sup>77</sup> R. N. Naylor, G. Shaw, D. V. Wilson, and D. N. Butler, *J. Chem. Soc.* 4845 (1961).

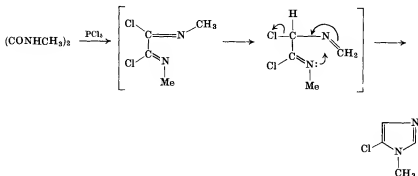
<sup>78</sup> J. Heinze, H. Bäumgartel, and H. Zimmermann, *Ber.* **101**, 3504 (1968).



## C. FORMATION OF THE 1:2- OR 1:5-BOND



The Wallach synthesis<sup>79</sup> involves ring closure of an *N,N'*-disubstituted oxamide with  $\text{PCl}_5$  to give a chlorine-containing compound, which, on reduction with hydriodic acid, yields a 1-substituted imidazole. The method has been adapted for the formation of halogen-substituted imidazoles.<sup>80-82</sup>



Ring closure of acylamines prepared from ethylenediamine also yields imidazoles,<sup>83</sup> but this reaction will be discussed in Section II, E as formation of the 1:2- and 2:3-bonds. When 2,2'-dipyridyl compounds react with methylene iodide,<sup>84</sup> bromine in pyridine, or *p*-toluenesulfonyl chloride in pyridine,<sup>85</sup> imidazolium salts are produced.

<sup>79</sup> O. Wallach and E. Schulze, *Ber.* **14**, 420 (1881).

<sup>80</sup> E. F. Godefroi, C. A. M. van der Eycken, and P. A. J. Janssen, *J. Org. Chem.* **32**, 1259 (1967).

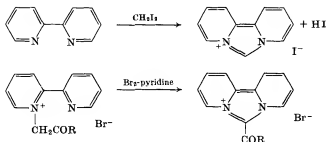
<sup>81</sup> P. M. Kochergin, *Zh. Obshch. Khim.* **34**, 3402 (1964); *Chem. Abstr.* **62**, 4022 (1965).

<sup>82</sup> P. M. Kochergin and R. M. Palei, *Zh. Obshch. Khim.* **38**, 1132 (1968).

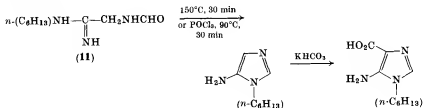
<sup>83</sup> H. Kroeper and J. Sand, Belgian Patent 661,322 (1965); *Chem. Abstr.* **64**, 2094 (1966).

<sup>84</sup> J. C. Calder and W. H. F. Sasse, *Australian J. Chem.* **18**, 1819 (1965).

<sup>85</sup> J. C. Calder and W. H. F. Sasse, *Australian J. Chem.* **21**, 1023 (1968).



Cusack *et al.*<sup>86</sup> have synthesized 5-aminoimidazoles by ring closure of formylglycine amidines (**11**) induced by heating or with phosphoryl chloride.



Methyl  $\beta$ -hydroxypropionimidates (**12**) (prepared from ethylene cyanohydrin, methanol, and HCl) condense with aminoacetaldehyde dimethylacetal (**13**) to yield an amidine hydrochloride (**14**) which undergoes ring closure to an imidazole.<sup>87</sup> Applications of this reaction have been used in the synthesis of 2-phenylimidazole and its 4-alkyl derivatives,<sup>88</sup> some new 2-mercaptoimidazoles,<sup>89</sup> and "isohistamine".<sup>90</sup> Isohistamine [2-(2'-aminoethyl)imidazole], originally reported in error by Jones,<sup>91</sup> was prepared in 50% yield by an adaptation of the method of Ellinger and Goldberg<sup>92</sup> and proved by NMR spectroscopy to be the authentic compound. The compound prepared

<sup>86</sup> N. J. Cusack, G. J. Litchfield, and G. Shaw, *Chem. Commun.* 799 (1967).

<sup>87</sup> J. K. Lawson, *J. Am. Chem. Soc.* **75**, 3398 (1953); U.S. Patent 2,710,870 (1955); *Chem. Abstr.* **50**, 6514 (1956).

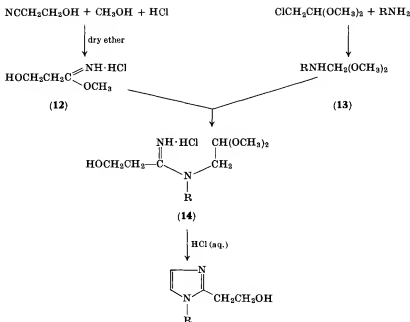
<sup>88</sup> A. J. Lawson, *J. Chem. Soc.* 4225 (1957).

<sup>89</sup> J. R. Geigy A.-G., Netherlands Patent 6,614,088 (1967); *Chem. Abstr.* **68**, 68993 (1968).

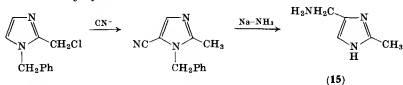
<sup>90</sup> G. J. Durant, M. E. Footitt, G. R. Ganellin, J. M. Loynes, E. S. Pepper, and A. M. Roe, *Chem. Commun.* 108 (1968).

<sup>91</sup> R. G. Jones, *J. Am. Chem. Soc.* **71**, 383 (1949).

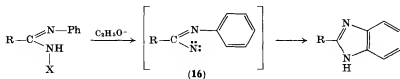
<sup>92</sup> L. P. Ellinger and A. A. Goldberg, *J. Chem. Soc.* 263 (1949).



by Jones<sup>91</sup> proved to be 2-methyl-4-aminomethylimidazole (15) formed by a rarely observed substitution with rearrangement ( $\text{S}_{\text{N}}1$ ) of chlorine by cyanide.<sup>90</sup>

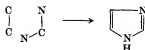


It has been suggested<sup>92</sup> that the formation of benzimidazoles from the cyclization of *N*-haloamidines with sodium ethoxide proceeds through a nitrene intermediate (16).

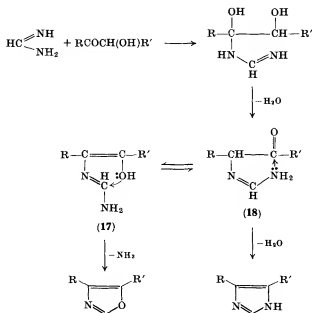


<sup>92</sup> V. J. Grenda, R. E. Jones, G. Gale, and M. Sletzing, *J. Org. Chem.* **30**, 259 (1965).

## D. FORMATION OF THE 1:5- AND 3:4-BONDS



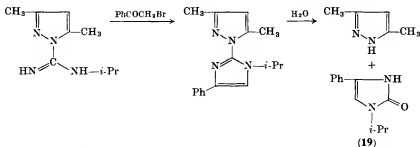
Formamidine reacts with  $\alpha$ -hydroxyketones<sup>65</sup> and  $\alpha$ -haloketones<sup>62</sup> to yield oxazoles and imidazoles. Normally the formamidine is liberated from its hydrochloride by the addition of sodium butoxide in *n*-butanol. It is interesting to note that in the reaction with  $\alpha$ -hydroxyketones, the aliphatic acyloins yielded mainly imidazoles (35–68% yield), whereas the benzoines gave mainly oxazoles (67–80%).<sup>65</sup> Unlike formamidine, acetamidine and benzamidine react with both aliphatic acyloins and with benzoines to yield imidazoles exclusively.<sup>66</sup> Bredereck<sup>65</sup> explains the reactions as follows:



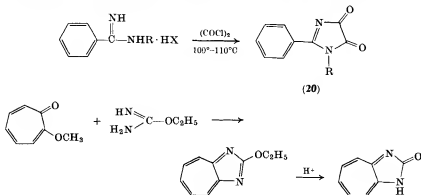
It is suggested that the aromatic groups favor the structure (17) derived from the enediol form of the hydroxyketone (and hence

oxazoles are the major reaction product), whereas aliphatic groups favor (18) and yield imidazoles mainly. The observation that higher amidines give imidazoles only is explained by the steric hindrance to reaction of enolic oxygen with the amidine carbon atom. The reaction between trisformylaminomethane and butyrolin yields a mixture of 4,5-dipropyloxazole (50%) and 4,5-dipropylimidazole (25%).<sup>65</sup>

1-Isopropyl-4-phenylimidazol-2-one (19) has been prepared in 51% yield from an amidine,<sup>94</sup> while Krieg *et al.*<sup>95</sup> utilized the method to



prepare 4-alkyl-2,5-diarylimidazoles. Goerdeler and Sappelt<sup>96</sup> extended this reaction to the synthesis of an imidazoline-4,5-dione (20) from an *N*-substituted benzamidine and oxalyl chloride, while Sunagawa and Watatani<sup>97</sup> used a similar method to prepare cyclo-



<sup>94</sup> G. Losse, A. Barth, and R. Sachadae, *Ber.* **94**, 467 (1961).

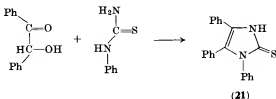
<sup>95</sup> B. Krieg, L. Brandt, B. Carl, and G. Manecke, *Ber.* **100** 4042 (1967).

<sup>96</sup> J. Goerdeler and R. Sappelt, *Ber.* **100**, 2064 (1967).

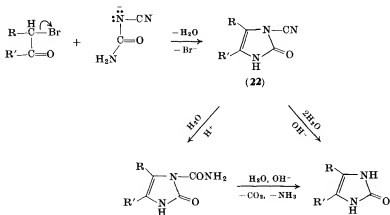
<sup>97</sup> G. Sunagawa and W. Watatani, *Chem. Pharm. Bull. Japan* **16**, 1300, 1308 (1968).

heptimidazol-2(1*H*)-one derivatives. Aminomalononitrile reacts with formamidine acetate to yield 4-cyano-5-aminoimidazole.<sup>98</sup> When amidines are disubstituted on nitrogen, imidazolines are the products.<sup>99</sup>

The reaction of urea (and thiourea) derivatives with  $\alpha$ -hydroxyketones yields imidazoles. Thus, condensation of benzoin with *N*-phenylthiourea in hexanol in the presence of catalytic quantities of HCl (or dry HCl) gives 1,4,5-triphenylimidazole-2-thione (**21**) in 50–60% yield.<sup>100</sup>



In similar fashion cyanourea reacts with  $\alpha$ -haloketones to yield 1-cyano-2-imidazolones (**22**).<sup>101</sup>



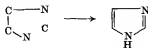
<sup>98</sup> J. P. Ferris and L. E. Orgel, *J. Am. Chem. Soc.* **87**, 4976 (1965).

<sup>99</sup> W. Theilacker and D. Arlt, German Patent 1,234,208 (1967); *Chem. Abstr.* **67**, 2898 (1967).

<sup>100</sup> P. M. Kochergin, V. E. Bogachev, and M. G. Fomenko, Russian Patent 137,517 (1960); *Chem. Abstr.* **56**, 475 (1962).

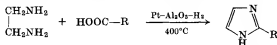
<sup>101</sup> H. Beyer and H. Schilling, *Ber.* **99**, 2110 (1966).

## E. FORMATION OF THE 1:2- AND 2:3-BONDS



The reaction of  $\alpha$ -hydroxylaminodioximes or  $\alpha$ -dioximes with aldehydes provides a route to the formation of 1-hydroxyimidazole-3-oxides<sup>102</sup> (see Section II, F).

One of the most widely used methods involving formation of the 1:2- and 2:3-bonds is the reaction of an alkylene polyamine with the appropriate alcohol, aldehyde, or fatty acid at high temperature in the presence of a dehydrogenating agent such as  $\text{Pt}/\text{Al}_2\text{O}_3$ .<sup>103, 104</sup> Although yields are high, the procedure is rather complicated experimentally. Recent modifications<sup>83, 105</sup> have allowed manufacture of



the parent base, imidazole. The reaction of *o*-phenylenediamine with a fatty acid followed by dichromate oxidation leads to 2-substituted imidazole-4,5-dicarboxylic acids<sup>106</sup> (which can be readily decarboxylated by heating). A French patent<sup>107</sup> describes the purification of the products of the foregoing reactions by azeotropic distillation with an alkylaromatic hydrocarbon which boils  $10^\circ\text{--}40^\circ\text{C}$  lower than the imidazole. Thus, 2-methylimidazole can be purified by distillation with 1- or 2-methylnaphthalene, and then isolated by washing with toluene or pentane. Taylor and Yoneda<sup>108</sup> have recently used the above reaction for the synthesis of some benzimidazole derivatives.

<sup>102</sup> G. La Parola, *Gazz. Chim. Ital.* **75**, 216 (1945); L. B. Volodarsky, A. N. Lisak, and V. A. Koptug, *Tetrahedron Letters* 1565 (1965).

<sup>103</sup> S. E. Voltz, J. H. Krause, and W. E. Erner, U.S. Patent 2,891,965 (1959); *Chem. Abstr.* **54**, 1557 (1960).

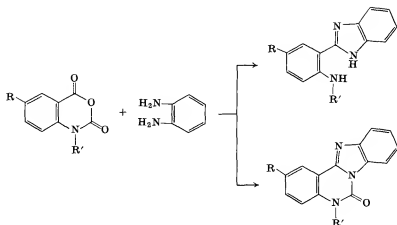
<sup>104</sup> H. A. Green, U.S. Patent 3,037,028 (1962); *Chem. Abstr.* **57**, 12501 (1962).

<sup>105</sup> H. A. Green, U.S. Patent 3,255,200 (1966); *Chem. Abstr.* **65**, 5467 (1966).

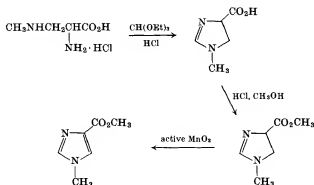
<sup>106</sup> P. M. Kochergin, A. M. Tsyganova, L. S. Blinova, and V. S. Shlikhunova, *Khim. Geterotsikl. Soedin., Akad. Nauk. Latv. SSR* 875 (1965); *Chem. Abstr.* **64**, 12660 (1966).

<sup>107</sup> Air Products and Chemicals Inc., French Patent 1,362,689 (1964); *Chem. Abstr.* **61**, 13317 (1964).

<sup>108</sup> E. C. Taylor and F. Yoneda, *Angew. Chem. Intern. Ed. Engl.* **6**, 878 (1967).



The specific synthesis of 1,4- and 1,5-substituted imidazoles<sup>109</sup> in 70% yields can be accomplished by cyclization of  $\alpha$ -amino- $\beta$ -methylaminopropionic acid (or  $\alpha$ -methylamino- $\beta$ -aminopropionic acid) in triethylorthoformate with a catalytic amount of hydrochloric acid, followed by dehydrogenation, under mild conditions, of the resulting 2-imidazoline.



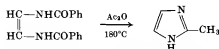
A reaction restricted to the synthesis of 2,4-disubstituted imidazoles is that between  $\alpha$ -aminonitriles and aldehydes.<sup>110</sup> The same bonds

<sup>109</sup> P. K. Martin, H. R. Matthews, H. Rapoport, and G. Thyagarajan, *J. Org. Chem.* **33**, 3758 (1968).

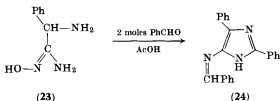
<sup>110</sup> S. S. Minovici, *Ber.* **29**, 2097 (1896); *Brit. Abstr.* **189**, 703 (1896).



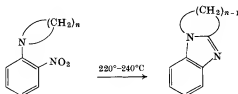
are formed when bis-*N*-benzoyl-1,2-diaminoethylenes react with acetic anhydride or other anhydrides.<sup>111</sup>



When aldehydes condense with 2-amino-2-phenylacet-amidoxime (23) derivatives of 5-aminoimidazole (24) are formed in high ( $\approx 80\%$ ) yield.<sup>112</sup>



Condensed imidazoles are formed in excellent yield when aromatic nitro compounds, substituted in the ortho position with an *N*-heteroparaffinic substituent, are cyclized using various reducing agents such as metal oxalates, iron pentacarbonyl, triethylphosphite,<sup>113</sup> or titanous chloride.<sup>114</sup> The same reaction takes place under



pyrolysis conditions<sup>115</sup> or by photochemical cyclization.<sup>113</sup> The corresponding azido and acylamido analogs of the nitro compounds can also be converted to imidazoles by oxidative ring closure with performic acid.<sup>113</sup>

<sup>111</sup> A. Windaus and W. Langenbeck, *Ber.* **55**, 3706 (1922).

<sup>112</sup> J. Barrans, *Compt. Rend. Soc. Biol.* **258**, 6185 (1964); *Chem. Abstr.* **61**, 7003 (1965).

<sup>113</sup> H. Suschitzky and M. E. Sutton, *J. Chem. Soc. C* 3058 (1968).

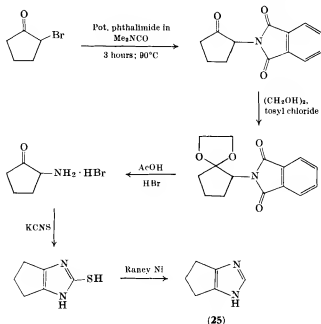
<sup>114</sup> H. Suschitzky and M. E. Sutton, *Tetrahedron* **24**, 4581 (1968).

<sup>115</sup> H. Suschitzky and M. E. Sutton, *Tetrahedron Letters* 3933 (1967).

## F. FORMATION OF THE 1:5- AND 2:3-BONDS



The Marckwald synthesis<sup>116</sup> employed the reaction of  $\alpha$ -amino ketones with cyanates, thiocyanates, and isothiocyanates to yield 3*H*-imidazol-2-ones or 3*H*-imidazole-2-thiones which are readily converted into imidazoles. The chief limitation of this method, which has been discussed adequately in earlier reviews,<sup>1-3</sup> is in the synthesis of the  $\alpha$ -aminocarbonyl compounds. The most convenient procedure is by reduction with sodium amalgam of  $\alpha$ -amino acids.<sup>117</sup> Among recent applications of the method<sup>118, 119</sup> is the synthesis<sup>118</sup> of 4,5-



<sup>116</sup> W. Marckwald, *Ber.* **25**, 2354 (1892).

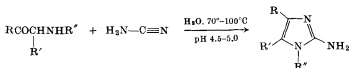
<sup>117</sup> A. J. Lawson and H. V. Morley, *J. Chem. Soc.* 1695 (1955); 566 (1957).

<sup>118</sup> H. Schubert, B. Ruchberg, and G. Fiedrich, *J. Prakt. Chem.* **32**, 249 (1966); *Chem. Abstr.* **65**, 18575 (1966).

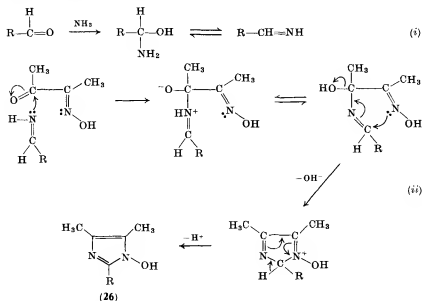
<sup>119</sup> A. Lespagnol, C. Lespagnol, P. Marcinal, M. Brunaud, and J. Salle, *Chim. Ther.* **66**, 292 (1966); *Chem. Abstr.* **67**, 3035 (1967).

trimethyleneimidazole (25). The same compound was also prepared from cyclopentanone oxime.<sup>118</sup>

Reaction of  $\alpha$ -aminoketones<sup>120</sup> (or their acetals<sup>121</sup>) with cyanamide, followed by hydrolysis and ring closure leads to 2-aminoimidazoles.



When an isonitrosoketone reacts with an aldoxime, the product is an imidazole *N*-oxide.<sup>122</sup> In a similar reaction Allan and Allan<sup>123</sup> prepared 1-hydroxyimidazoles by the reaction of 2,3-butanedione-monoxime with aldehydes in aqueous ammonia. The overall reaction is undoubtedly the reaction of the isonitrosoketone with an aldimine by a mechanism similar to the following:



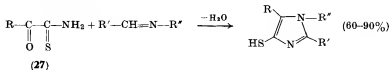
<sup>120</sup> A. Lawson, *J. Chem. Soc.* 307 (1956).

<sup>121</sup> Lepetit, S.p.A., Netherlands Patent 6,604,949 (1966); *Chem. Abstr.* **66**, 78011 (1967).

<sup>122</sup> K. Bodendorf and H. Towliati, *Arch. Pharm.* **298**, 293 (1965); *Chem. Abstr.* **63**, 5629 (1965); J. B. Wright, *J. Org. Chem.* **29**, 1620 (1964).

<sup>123</sup> F. J. Allan and G. G. Allan, *Chem. Ind. (London)* 1837 (1964).

The *N*-hydroxy structure (26) was preferred<sup>123</sup> to an *N*-oxide representation on account of the amphoteric nature of the product and because the derived acetate formed a well-defined hydrochloride salt. Hydrogenation of these *N*-hydroxyimidazoles over Raney nickel gives imidazoles in 60–94% yields.<sup>122</sup> The reaction has been adapted for the preparation of 4-mercaptoimidazoles, using an  $\alpha$ -ketothionamide (27) with an aldimine.<sup>124</sup>



### G. DEHYDROGENATION OF IMIDAZOLINES

Imidazoles have been prepared by dehydrogenation of imidazolines<sup>125–127</sup> (e.g., dehydrogenation of 2-methylimidazoline with Raney nickel at 170°–200°C<sup>125</sup>), and a number of the foregoing procedures (e.g., from *N,N'*-disubstituted amidines<sup>94</sup> and from  $\alpha$ -diamines<sup>103–106</sup>) involve initial formation of imidazolines. The condensation of ephedrone and other  $\alpha$ -aminoketones with carbonyl compounds and ammonia yields 3-imidazolines which can be dehydrogenated with sulfur to form imidazoles.<sup>128</sup> Similarly, the preparation of 2-substituted benzimidazoles from *o*-phenylenediamine with aliphatic or aliphatic–aromatic ketones<sup>129–131</sup> also progresses via an imidazoline stage. Imidazole-2-thiones can be prepared from 2-thiohydantoins.<sup>132</sup>

<sup>124</sup> H. Offermanns, P. Krings, and F. Asinger, *Tetrahedron Letters* **15**, 1809 (1968).

<sup>125</sup> M. Ya. Kraft, P. M. Kochergin, A. M. Tysganova, and V. S. Shlikhunova, USSR Patent 176,912 (1965); *Chem. Abstr.* **64**, 12684 (1966).

<sup>126</sup> N. Sawa, S. Kishizoe, and Y. Tsujino, Japanese Patent 26,405 (1964); *Chem. Abstr.* **62**, 9142 (1965).

<sup>127</sup> M. Ya. Kraft, P. M. Kochergin, A. M. Tysganova, V. S. Shlikhunova, I. A. Kuznetsova, E. N. Alekseeva, and S. Ordzhonikidze, USSR Patent 201,418 (1967); *Chem. Abstr.* **69**, 19158 (1968).

<sup>128</sup> E. Jaassmann and H. Schulz, *Pharmazie* **18**, 461 (1963); *Chem. Abstr.* **64**, 3518 (1966).

<sup>129</sup> R. C. Elderfield and J. R. McCarthy, *J. Am. Chem. Soc.* **73**, 975 (1951).

<sup>130</sup> R. C. Elderfield and V. B. Meyer, *J. Am. Chem. Soc.* **76**, 1883, 1887 (1954).

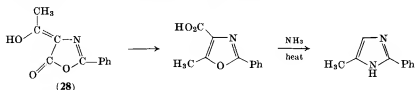
<sup>131</sup> R. C. Elderfield and K. L. Burgess, *J. Am. Chem. Soc.* **82**, 1975 (1960).

<sup>132</sup> J. E. Scott, *Biochem. J.* **107**, 16P–17P (1968).

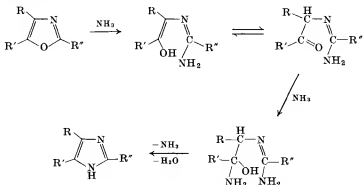
In spite of the high degree of resonance stabilization of the imidazole ring, dehydrogenation is a difficult procedure. The use of metals such as Ni, Pt, or Pd, high temperature, or hydrogen acceptors such as S, Se, CuO, or cyclohexanone have proved effective. Mild oxidation with active manganese dioxide allows dehydrogenation of substituted 2-imidazolines in high yield.<sup>109</sup>

## H. FROM OTHER HETEROCYCLES

It has been known for many years that treatment of oxazoles with ammonia (or amines) results in their conversion into imidazoles.<sup>133-134</sup> Similarly, 4-hydroxymethylene-5-oxazolones (**28**) yield (decarboxylated) imidazoles under the same conditions.<sup>135</sup>



When formamide is used in place of ammonia yields are reported<sup>61, 71</sup> to lie in the 50–90% range. The reaction fails<sup>65</sup> only with benzoxazole and 2,4,5-triethyloxazole. Electron-withdrawing substituents on the oxazole ring facilitate imidazole formation, probably by lowering the electron density at the oxygen atom. The following reaction course has been proposed<sup>65</sup>:

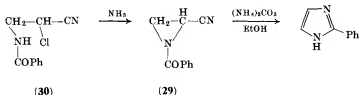


<sup>133</sup> H. Bredereck, R. Gompper, and H. Wild, *Ber.* **88**, 1351 (1955).

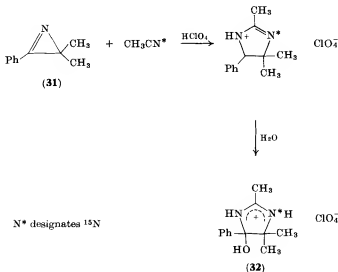
<sup>134</sup> J. W. Cornforth and R. H. Cornforth, *J. Chem. Soc.* **96** (1947).

<sup>135</sup> J. W. Cornforth and H. T. Huang, *J. Chem. Soc.* **1960** (1948).

A 25% yield of 2-phenylimidazole has been obtained<sup>136</sup> by the action of ammonium carbonate in ethanol on 1-benzoyl-2-cyanoaziridine (29) [from the reaction of  $\alpha$ -chloro- $\beta$ -benzoylamino propionitrile (30) with liquid ammonia]. Imidazolium salts have been isolated from



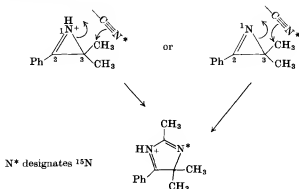
the reaction of azirines with perchloric acid and acetonitrile.<sup>137</sup> Thus, 3,3-dimethyl-2-phenyl-1-azirine (31) produces a 77% yield of 4-hydroxy-4-phenyl-2,5,5-trimethyl-2-imidazolium perchlorate (32). Results from labeling the nitrogen of acetonitrile are consistent with



<sup>136</sup> R. Wakasa and G. Inoue, Japanese Patent 9152 (1965); *Chem. Abstr.* **63**, 4305 (1965).

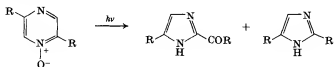
<sup>137</sup> N. J. Leonard and B. Zwanenburg, *J. Am. Chem. Soc.* **89**, 4456 (1967).

the following possible mechanisms:

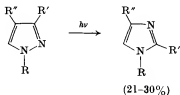


It is likely that there is 1,3-bond cleavage and ring enlargement at the cleavage site as no products were isolated consistent with nucleophilic attack at the 1,2-bond.<sup>137</sup>

Various photochemical reactions have been found to produce imidazoles, although the majority of these are not of synthetic importance. Ultraviolet irradiation of pyrazine *N*-oxides<sup>138</sup> produces 2-acyl- and 2-alkylimidazoles.



*N*- or *C*-alkylated pyrazoles can also undergo photorearrangement to imidazoles<sup>139</sup> in moderate yield. Indazoles similarly rearrange to benzimidazoles.

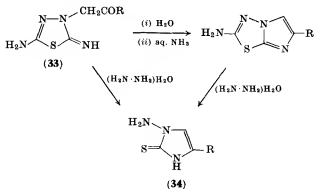


<sup>138</sup> N. Ikekawa and Y. Honma, *Tetrahedron Letters* 1197 (1967).

<sup>139</sup> von H. Tiefenthaler, W. Dörscheln, H. Göth, and H. Schmid, *Helv. Chim. Acta* **50**, 2244 (1967).

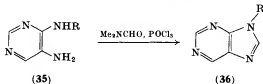
Reduction of 2,4,6-triphenyltriazine gives 2,4,5-triphenylimidazole,<sup>140</sup> while the 1,2,4-triazine ring also contracts to an imidazole<sup>141</sup> with zinc dust and acetic acid. Treatment of 2,5-diaminothiazoles with alkali leads to imidazole-2-thiones.<sup>142, 143</sup>

Treatment of 2,5-diamino-1,3,4-thiadiazole with an  $\alpha$ -haloketone in ethanol, followed by reaction of the resulting 2-imino-3-( $\alpha$ -keto-alkyl)-5-amino-1,3,4-thiadiazoline hydrohalide (**33**) with aqueous ammonia, and then excess of hydrazine hydrate, leads to 1-amino-imidazole-2-thiones (**34**).<sup>144</sup>



Ring transformation of 2-amino-3-phenacyl-1,3,4-oxadiazolium halides with amines, liquid ammonia, or heterocyclic bases yields 2-amino-1-acylamino-4-arylimidazoles.<sup>145</sup>

The method of Clarke and Lister<sup>146</sup> for the conversion of a pyrimidine (**35**) into a purine (**36**) is a ring-closure reaction which could be classified as formation of the 1:2- and 2:3-bonds.



<sup>140</sup> A. H. Cook and D. G. Jones, *J. Chem. Soc.* 278 (1941).

<sup>141</sup> R. Metze and G. Scherowsky, *Ber.* **92**, 2481 (1959).

<sup>142</sup> A. H. Cook, J. D. Downer, and Sir I. Heilbron, *J. Chem. Soc.* 2028 (1948).

<sup>143</sup> A. H. Cook, Sir I. Heilbron, and E. Smith, *J. Chem. Soc.* 1440 (1949).

<sup>144</sup> A. Sitte, H. Paul, and G. Hilgetg, *Z. Chem.* **7**, 341 (1967).

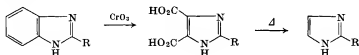
<sup>145</sup> A. Hetzheim, O. Peters, and H. Beyer, *Ber.* **100**, 3418 (1967).

<sup>146</sup> J. Clark and J. H. Lister, *J. Chem. Soc.* 5048 (1961).



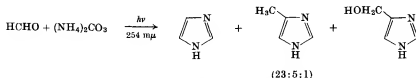
## I. FROM BENZIMIDAZOLES

Benzimidazoles are oxidized by chromic acid<sup>147</sup> or 30% hydrogen peroxide<sup>148</sup> to imidazole-4,5-dicarboxylic acids, which are readily decarboxylated.<sup>148</sup> It is interesting to note that *N*-substituted benzimidazoles cannot be converted into the imidazole dicarboxylic acids<sup>149</sup> and that the carboxyl groups can be removed one at a time.<sup>2</sup> During the decarboxylation of imidazole-1-*d*-4,5-dicarboxylic acid-*d*<sub>2</sub>, mass spectrometry shows<sup>150</sup> that deuterium atoms also appear on C-2, indicating that the ring hydrogen atoms are labile at elevated temperatures.



## J. OTHER METHODS

It has been reported<sup>151</sup> that, under the influence of ultraviolet radiation, aqueous solutions of formaldehyde and ammonium salts produce imidazole products. It is possible that the irradiation catalyzes



a "formose reaction"<sup>152-153</sup> yielding glycolaldehyde and trioses which could react with ammonia to produce the imidazoles which were identified.

<sup>147</sup> N. B. Vinogradova and N. V. Khromov-Borisov, *Zh. Obshch. Khim.* **31**, 1476 (1961); *Chem. Abstr.* **55**, 23502 (1961).

<sup>148</sup> H. v Euler, H. Hasselquist, and O. Heidenberger, *Arkiv Kemi.* **14**, 419 (1958); *Chem. Abstr.* **54**, 12156 (1960).

<sup>149</sup> L. S. Efros, N. V. Khromov-Borisov, L. R. Davidenkov, and M. M. Nedel, *Zh. Obshch. Khim.* **26**, 455 (1956); *Chem. Abstr.* **50**, 13881 (1956).

<sup>150</sup> R. Hodges and M. R. Grimmett, unpublished data.

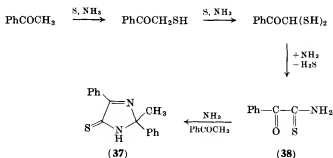
<sup>151</sup> V. S. Siderov, T. E. Pavlovskaya, and A. G. Pasynskii, *Zh. Evolyutsionnoi Biokhim. i Fiziol.* **2**, 293 (1966); *Chem. Abstr.* **66**, 37831 (1967).

<sup>152</sup> W. Langenbeck, *Angew. Chem.* **66**, 151 (1954).

<sup>153</sup> W. Langenbeck, *Tetrahedron* **3**, 185 (1958).

In some further "primitive life" experiments 4,5-dicyanoimidazole and adenine were formed in the reaction of HCN with liquid ammonia.<sup>154-156</sup>

The reaction of methylketones with sulfur and ammonia produces 4<sup>3</sup>-imidazoline-5-thiones (37) (especially in the presence of pyridine).<sup>157</sup> The initial stage of the reaction is formation of a phenylglyoxylic thionamide (38), followed by ring closure, and thus the reaction



closely resembles a previous method<sup>124</sup> described for the formation of the 1:5- and 2:3-bonds (Section II, F).

When diethylamine reacts with acetonitrile and sulfur in the presence of zinc powder, 2-methylimidazoline is formed<sup>126</sup> and may be dehydrogenated with nickel to 2-methylimidazole. Using the same method, 2-ethyl-, 2,4-dimethyl-, and 2-ethyl-4-methylimidazoles have been synthesized in yields of about 10%.<sup>126</sup>

Recent Japanese patents<sup>158</sup> relate to the preparation of 2,4,5-trimethylimidazole (and other *C*-substituted imidazoles) when 3-aminobut-1-yne is refluxed for 5 hours with acetamide. 3-Butynylthiourea (39) and 3-butynylurea are converted by concentrated sulfuric acid into 4,5-dimethylimidazole-2-thione (40) and 4,5-dimethyl-2-imidazolone, respectively. The latter compound is also

<sup>154</sup> H. Wakamatsu, Y. Yamada, T. Saito, I. Kumashiro, and T. Takenishi, *J. Org. Chem.* **31**, 2035 (1966).

<sup>155</sup> Y. Yamada, I. Kumashiro, and T. Takenishi, *J. Org. Chem.* **33**, 642 (1968).

<sup>156</sup> Y. Yamada, I. Kumashiro, and T. Takenishi, *Bull. Chem. Soc. Japan* **41**, 1237 (1968).

<sup>157</sup> F. Asinger and H. Offermanns, *Angew. Chem. Intern. Ed. Engl.* **6**, 907 (1967).

<sup>158</sup> Y. Yura, Japanese Patents 12938, 12939, 12940 (1964); *Chem. Abstr.* **62**, 565 (1965).



Imidazole has been formed by heating aminoamide resins.<sup>160</sup>

Catalytic conversion of acetylene, ammonia, and ethylenimine at 45°–50°C produces acetonitrile, 2-methylimidazoline, and 2-methylimidazole.<sup>161</sup>

A new method of synthesis<sup>162</sup> of the imidazole ring by the use of *N*-cyaniminodithiocarbonic esters (41) involves formation of the 4:5-bond. Reaction of (42) with KNCO in acetic acid yielded the corresponding amide (43) which was cyclized by sodium hydroxide to the substituted purine (44). Treatment of (42) with Raney nickel and hydrogen produced 4-amino-5-carbethoxy-1-methyl-4-imidazoline (45), which could also be cyclized to a purine (46).<sup>162</sup>

### III. Physical Properties

#### A. DIPOLE MOMENTS

When the ring has no polar substituents the dipole moments of imidazole and its derivatives are of the order of 3.8–4.0 D.<sup>163–165</sup> A nitro substituent in a condensed ring increases this value by 2.0–2.5 D,<sup>166</sup> whereas *N*-arylation lowers the dipole moment due to conjugation of the imidazole and aryl rings.<sup>167</sup> Further measurements<sup>168</sup> (from dielectric data in benzene at 25°C) have shown that in *N*-arylimidazoles, the phenyl ring is out of the plane of the imidazole

<sup>160</sup> J. Mleziva and A. Pánek, *Chem. Průmysl* **9**, 557 (1959); *Chem. Abstr.* **54**, 3387 (1960).

<sup>161</sup> F. Runge and H. Hummel, *Chem. Technol.* **3**, 163 (1951); *Chem. Abstr.* **46**, 2541 (1952).

<sup>162</sup> R. Gompper, M. Göng, and F. Saygin, *Tetrahedron Letters* 1885 (1966).

<sup>163</sup> O. A. Osipov, A. M. Simonov, V. I. Minkin, and A. D. Garnovskii, *Tr. Soveshch. po Fiz. Metodam Issled. Org. Soedin. i Khim. Protseessov, Akad. Nauk Kirg. SSR Inst. Organ. Khim., Frunze*, 1962 61 (1964); *Chem. Abstr.* **62**, 3494 (1965).

<sup>164</sup> V. I. Minkin, O. A. Osipov, A. D. Garnovskii, and A. M. Simonov, *Zh. Fiz. Khim.* **36**, 469 (1962); *Russ. J. Phys. Chem.* **36**, 245 (1962).

<sup>165</sup> K. A. Jensen and A. Friediger, *Kgl. Danske Videnskab. Selskab. Mat.-Fys. Medd.* **20**, 1 (1943); *Chem. Abstr.* **39**, 2068 (1945).

<sup>166</sup> O. A. Osipov, A. M. Simonov, V. I. Minkin, and A. D. Garnovskii, *Zh. Fiz. Khim.* **36**, 1466, (1962); *Russ. J. Phys. Chem.* **36**, 784 (1962).

<sup>167</sup> A. F. Pozharskii and A. M. Simonov, *Zh. Obshch. Khim.* **34**, 224 (1964); *Chem. Abstr.* **60**, 10517 (1964).

<sup>168</sup> L. M. Sitkina, A. F. Pozharskii, and A. M. Simonov, *Zh. Obshch. Khim.* **37**, 2215 (1967); *Chem. Abstr.* **68**, 113920 (1968).

ring. Neither *N*-alkylation<sup>164</sup> nor carbocyclic rings condensed with imidazole<sup>166</sup> have much effect on the dipole moment.

The magnitude of the dipole moment for imidazole indicates considerable polarization of the ring, although the extent of polarization is much less than that required to yield an ionic structure.

TABLE I  
DIPOLE MOMENTS OF IMIDAZOLES

Compound	D/(Debye units)	Reference <sup>a</sup>
Imidazole	3.99, 3.84	1-3
1-Propylimidazole	4.12	4
1-Phenylimidazole	3.14	4
4-Methylimidazole	6.2	5
4,5-Diphenylimidazole	4.34	1, 2
1-Ethyl-4,5-diphenylimidazole	4.11	1, 2
1-(2,4-Dinitrophenyl)imidazole	3.36	4
1-Propyl-4,5-diphenylimidazole	4.17	1, 2
1-Methyl-2-formylimidazole	3.77	6
1-Phenyl-2-formylimidazole	3.53	6
1-Benzyl-2-formylimidazole	3.37	6
Benzimidazole	3.93-4.08	1-3, 7
1-Methylbenzimidazole	4.04	1, 2
4,5,6,7-Tetrahydrobenzimidazole	3.93	1, 2
5(6)-Nitrobenzimidazole	6.57	8
1-Benzylbenzimidazole	3.47	4
1-Phenylbenzimidazole	3.37	4
1-Propylbenzimidazole	3.72	4

<sup>a</sup> KEY TO REFERENCES:

1. O. A. Osipov, A. M. Simonov, V. I. Minkin, and A. D. Garnovskii, *Tr. Soveshch. po Fiz. Metodam Issled. Org. Soedin. i Khim. Protessov, Akad. Nauk Kirg. SSR Inst. Organ. Khim., Frunze, 1962* 61 (1964); *Chem. Abstr.* **62**, 3494 (1965).
2. V. I. Minkin, O. A. Osipov, A. D. Garnovskii, and A. M. Simonov, *Zh. Fiz. Khim.* **36**, 469 (1962); *Russ. J. Phys. Chem.* **36**, 245 (1962).
3. K. A. Jensen and A. Friediger, *Kgl. Danske Videnskab. Selskab. Mat.-Fys. Medd.* **20**, 1 (1943); *Chem. Abstr.* **39**, 2068 (1945).
4. A. F. Pozharskii and A. M. Simonov, *Zh. Obshch. Khim.* **34**, 224 (1964); *Chem. Abstr.* **60**, 10517 (1964).
5. W. Hüchel and W. Jahnertz, *Ber.* **B74**, 652 (1941).
6. L. M. Sitkina, A. F. Pozharskii, and A. M. Simonov, *Zh. Obshch. Khim.* **37**, 2215 (1967); *Chem. Abstr.* **68**, 113920 (1968).
7. Ya. Syrkin and E. Shott-L'vova, *Acta Physicochim. URSS* **20**, 397 (1945); *Chem. Abstr.* **40**, 5310 (1946).
8. O. A. Osipov, A. M. Simonov, V. I. Minkin, and A. D. Garnovskii, *Zh. Fiz. Khim.* **36**, 1466 (1962); *Russ. J. Phys. Chem.* **36**, 784 (1962).

The dipole moment depends on concentration, a property typical of compounds containing the imino group and forming intermolecular hydrogen bonds.<sup>163</sup> Imidazole association can thus be explained by hydrogen-bond formation of the type N-H---N, and not by the formation of intermolecular ionic compounds of the ammonium-salt type. The association constant is 5-20 and not 2, as would be expected from an ionogenic structure.<sup>163</sup>

Dipole moment data also indicate<sup>169</sup> that the line of action of the moment in imidazole makes an angle of  $\sim 13^\circ$  with the *A* axis (where the proposed *A* axis makes an angle of  $\sim 28^\circ$  with the N-H bond and intersects the N-C bond joining the 1- and 2-positions). Rotation constants and moments of inertia determined by the same workers<sup>169</sup> indicate that the molecule is planar.

Pozharskii *et al.*<sup>3</sup> have criticized the high dipole moments obtained by Hückel<sup>170</sup> for imidazole and 4-methylimidazole, suggesting that the measurements were made in concentrated solutions where association would be significant. A similar conclusion had been reached by earlier workers<sup>171</sup> (see Table I).

### B. MELTING POINTS, BOILING POINTS, AND SOLUBILITIES

As a general rule, the boiling points of imidazoles are relatively high unless a substituent has been introduced into the 1-position (e.g., imidazole, b.p.  $256^\circ\text{C}$ ; 4-methylimidazole, b.p.  $264^\circ\text{C}$ ; and 1-methylimidazole, b.p.  $198^\circ\text{C}$ ). Molecular association through the imino NH is undoubtedly one of the major factors responsible for the high boiling points.

A similar pattern is evident with melting points. (e.g., imidazole, m.p.  $90^\circ\text{C}$ ; 4-methylimidazole, m.p.  $56^\circ\text{C}$ ; and 1-methylimidazole, m.p.  $-6^\circ\text{C}$ ).

Imidazoles in which the imino hydrogen is available for intermolecular hydrogen bonding are soluble in polar and rather insoluble in nonpolar solvents. The solubilities of imidazole in benzene and dioxane and of 4-methylimidazole in benzene have been measured.<sup>172</sup>

<sup>169</sup> J. H. Griffiths, A. Wardley, V. E. Williams, N. L. Owen, and J. Sheridan, *Nature* **216**, 1301 (1967).

<sup>170</sup> W. Hückel and W. Jahneutz, *Ber.* **B74**, 652 (1941).

<sup>171</sup> K. A. Jensen and A. Friediger, *Kgl. Danske Videnskab. Selskab. Math.-Fys. Medd.* **20**, 1 (1943); *Chem. Abstr.* **39**, 2069 (1945).

<sup>172</sup> W. Hückel, J. Datow, and E. Simmersbach, *Z. Phys. Chem.* **186A**, 129 (1940); *Chem. Abstr.* **35**, 1688 (1941).

When imidazoles are substituted in the 1-position the solubility characteristics are reversed.

### C. ACID AND BASIC STRENGTH

Imidazoles are amphoteric compounds with a basic, "pyridine-type" nitrogen (they are about  $10^6$  times more basic than oxazoles and  $10^4$  times more basic than thiazoles<sup>173</sup>), and (where the NH is unsubstituted) a weakly acidic, "pyrrole-type" amino nitrogen in the ring. In consequence, imidazoles readily form salts with acids and often form salts (or complexes) with metals. The sparingly soluble silver salts formed by imidazoles have been used by Giesemann *et al.*<sup>174</sup> as intermediates in the synthesis of 1-triphenylmethylimidazoles. Normally, however, the salts formed with acids are more important in isolation and purification procedures.

The effects of substituents on the acidic and basic strengths of imidazoles have been discussed by Hofmann<sup>1</sup> and Pozharskii *et al.*<sup>3</sup> in previous reviews. Precise data have been determined<sup>175</sup> for the basicity of imidazole in  $D_2O-H_2O$  mixtures. Perrin<sup>176</sup> has developed methods based on the Hammett equation for predicting the  $pK_a$  values in water of substituted imidazoles (and other heterocycles), while applications of the Hammett equation have also been made to 2-substituted imidazoles.<sup>177</sup> Calculations of  $pK$  values for 2-aminoimidazolium ions suggest that 2-aminoimidazoles are better regarded

TABLE II  
BASIC  $pK$  VALUES OF IMIDAZOLES

Compound	$pK_a$	Compound	$pK_a$
Imidazole	6.95 <sup>a</sup>	1-Ethylimidazole	7.30 <sup>c</sup>
4-Methylimidazole	7.61 <sup>b</sup>	2-Ethylimidazole	8.00 <sup>c</sup>
2-Methylimidazole	7.85 <sup>c</sup>	4-Hydroxymethylimidazole	6.54 <sup>b</sup>
1-Methylimidazole	~ 7.0 <sup>c</sup>	4-(2-Hydroxyethyl)-imidazole	7.26 <sup>b</sup>
2,4-Dimethylimidazole	~ 8.5 <sup>c</sup>		
2,4,5-Trimethylimidazole	8.92 <sup>c</sup>		

<sup>173</sup> P. Haake and L. P. Bausher, *J. Phys. Chem.* **72**, 2213 (1968).

<sup>174</sup> H. Giesemann, H. Lettau, and H.-G. Mannsfeldt, *Ber.* **93**, 570 (1960).

<sup>175</sup> L. Pentz and E. R. Thornton, *J. Am. Chem. Soc.* **89**, 6931 (1967).

<sup>176</sup> D. D. Perrin, *J. Chem. Soc.* 5590 (1965).

<sup>177</sup> M. Charton, *J. Org. Chem.* **30**, 3346 (1965).

TABLE II—continued

Compound	p <i>K</i> <sub>a</sub>	Compound	p <i>K</i> <sub>a</sub>
4-Acetoxymethylimidazole	6.20 <sup>b</sup>	Imidazole-4,5-dicarboxylic acid	2.93 <sup>f</sup>
4-(2-Acetoxyethyl)-imidazole	6.97 <sup>b</sup>	2-Methylimidazole-4,5-dicarboxylic acid	4.25 <sup>f</sup>
1-Acetylimidazole	3.6 <sup>c</sup>	2-Phenylimidazole-4,5-dicarboxylic acid	3.00 <sup>f</sup>
2-Phenylimidazole	6.48 <sup>c</sup>	Imidazole-4-carboxylic acid <sup>g</sup>	6.08 <sup>h</sup>
4-Phenylimidazole	6.10 <sup>c</sup>	4-Carbethoxyimidazole <sup>g</sup>	3.66 <sup>h</sup>
2,4-Diphenylimidazole	5.64 <sup>c</sup>	4-Bromimidazole <sup>g</sup>	3.60 <sup>h</sup>
2-(2-Imidazolyl)-imidazole	4.53 <sup>c</sup>	2-Nitroimidazole	-0.81 <sup>i</sup>
4-Nitroimidazole	-0.05 <sup>c</sup>	2-Aminoimidazole	8.46 <sup>j</sup>
1-Methyl-4-nitroimidazole	-0.53 <sup>c</sup>	1-Methyl-2-nitroimidazole	-0.44 <sup>i</sup>
1-Methyl-5-nitroimidazole	2.13 <sup>c</sup>	2-Amino-1-methylimidazole	8.65 <sup>j</sup>
1-Methyl-4-chloroimidazole	6.23 <sup>c</sup>	Benzimidazole	5.53 <sup>k</sup>
1-Methyl-4-phenylimidazole	5.78 <sup>c</sup>	Naphth[1,2- <i>d</i> ]imidazole	5.24 <sup>l</sup>
4-Carbamoylimidazole	3.7 <sup>c</sup>	2-Ethylbenzimidazole	6.23 <sup>k</sup>
4-(2-Aminoethyl)imidazole	9.8, 6.0 <sup>c</sup>	2-Isopropylbenzimidazole	6.21 <sup>k</sup>
4-Aminomethylimidazole	9.68, 5.88 <sup>c</sup>	2-Methyl-5(6)-nitrobenzimidazole	4.37 <sup>k</sup>
4-(2-Pyridyl)imidazole	5.42 <sup>c</sup>	2-Methyl-5,6-dinitrobenzimidazole	~0.7 <sup>k</sup>
5-Amino-4( <i>N</i> -methylcarboxamido)imidazole	9.5 <sup>c</sup>	4-Nitrobenzimidazole	3.33 <sup>k</sup>
4-(3-Carbamoylpropyl)-imidazole	6.52 <sup>c</sup>	5,6-Dimethylbenzimidazole	6.09 <sup>k</sup>
4-(3-Methoxycarbonylpropyl)imidazole	6.8 <sup>c</sup>	5-Aminobenzimidazole	6.07 <sup>k</sup>
Imidazole-4-aldehyde	2.90 <sup>d</sup>		
4,5-Dicyanoimidazole	5.2 <sup>e</sup>		

<sup>a</sup> A. H. M. Kirby and A. Neuberger, *Biochem. J.* **32**, 1146 (1938).<sup>b</sup> F. Schneider, *Z. Physiol. Chem.* **338**, 131 (1964); *Chem. Abstr.* **62**, 11905 (1965).<sup>c</sup> D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution." Butterworths, London (1965).<sup>d</sup> K. Broeklehurst and J. R. Griffiths, *Tetrahedron* **24**, 2407 (1968).<sup>e</sup> Y. Yamada, I. Kumashiro, and T. Takenishi, *Bull. Chem. Soc. Japan* **41**, 1237 (1968).<sup>f</sup> R. P. Saper, *Glasnik Hem. Crustva, Beograd.* **25-26** (5-7), 287 (1960-1961); *Chem. Abstr.* **59**, 1196 (1963).<sup>g</sup> Measurements in 23.3% aqueous ethanol at 30°C.<sup>h</sup> R. W. Cowgill and W. M. Clark, *J. Biol. Chem.* **198**, 33 (1952).<sup>i</sup> G. G. Gallo, C. R. Pasqualucci, P. Radelli, and G. Lancini, *J. Org. Chem.* **29**, 862 (1964).<sup>j</sup> B. T. Storey, W. W. Sullivan and C. L. Moyer, *J. Org. Chem.* **29**, 3118 (1964).<sup>k</sup> D. D. Perrin, *J. Chem. Soc.* 5590 (1965).<sup>l</sup> D. J. Brown, *J. Chem. Soc.* 1974 (1958).



as substituted imidazoles than as guanidine derivatives,<sup>178</sup> e.g., 2-aminoimidazole  $pK_a$ : 8.46 (in 0.1 *M* KCl), 8.39 (in 0.1 *M* KCl–C<sub>2</sub>H<sub>5</sub>OH [1:1]; cf. imidazole  $pK_a$  values: 7.01 and 6.34 (see Tables II and III).

TABLE III  
ACID  $pK$  VALUES OF IMIDAZOLES

Compound	$pK$
Imidazole	14.52 <sup>a</sup>
2-Phenylimidazole	13.32 <sup>b</sup>
4-Phenylimidazole	13.42 <sup>b</sup>
2,4-Diphenylimidazole	12.53 <sup>b</sup>
Imidazole-4-aldehyde	10.66 <sup>c</sup>
4-Nitroimidazole	9.30 <sup>b</sup>
Benzimidazole	13.2 <sup>a</sup>
Naphth[1,2- <i>d</i> ]imidazole	12.52 <sup>a</sup>

<sup>a</sup> D. J. Brown, *J. Chem. Soc.* 1974 (1958).

<sup>b</sup> D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London (1965).

<sup>c</sup> K. Brocklehurst and J. R. Griffiths, *Tetrahedron* **24**, 2407 (1968).

#### D. CRYSTAL STRUCTURE

Examination of the crystal structure of imidazole,<sup>179</sup> involving measurement of the bond lengths, shows considerable double-bond character in all bonds and demonstrates the presence of NH---N bonds with the exceptionally short length of 2.86 Å forming chains of molecules along the *c* axis. The crystals appear fibrous because of this chain formation.<sup>180</sup> Application of X-ray methods to the crystal structure of 4-methylimidazole<sup>181</sup> indicate a N–N distance of 3.0 Å.

<sup>178</sup> B. T. Storey, W. W. Sullivan, and C. L. Moyer, *J. Org. Chem.* **29**, 3118 (1964).

<sup>179</sup> S. Martinez-Carrera, *Acta Cryst.* **20**, 783 (1966); *Chem. Abstr.* **65**, 4762 (1966).

<sup>180</sup> G. Will, *Nature* **198**, 575 (1963).

<sup>181</sup> H. Zimmermann, *Ann.* **612**, 193 (1958); *Chem. Abstr.* **52**, 10683 (1958).

## E. ULTRAVIOLET SPECTRA

The observation that imidazole and its simple alkyl derivatives have little absorption in the near-ultraviolet can be attributed to their high aromatic stability. Alkyl groups introduced at any position in the imidazole ring produce a small bathochromic shift of the absorption band at 207–208  $m\mu$ .<sup>182–184</sup> When a ring carbon or nitrogen atom carries an aryl substituent new intense bands appear at 250–300  $m\mu$  due to conjugation with the aromatic systems.<sup>182, 184–187</sup>

Intense peaks also appear in the ultraviolet spectrum when a carbonyl function is conjugated with the imidazole ring as in the imidazole aldehydes,<sup>188–189</sup> carboxylic acids,<sup>76, 185</sup> and acylimidazoles.<sup>138</sup> Thus, imidazole 2-aldehyde has  $\lambda_{\max}$  285  $m\mu$  ( $\epsilon_{\max} = 12,500$  in ethanol)<sup>189</sup> imidazole-4-aldehyde (neutral molecule) has  $\lambda_{\max}$  257  $m\mu$  ( $\epsilon_{\max} = 11,900$ ), the corresponding cation has  $\lambda_{\max}$  238  $m\mu$  ( $\epsilon_{\max} = 7300$ ), and the anion has  $\lambda_{\max}$  281  $m\mu$  ( $\epsilon_{\max} = 16,900$ ),<sup>188</sup> and 2-acetyl-4-methylimidazole has  $\lambda_{\max}$  290  $m\mu$  ( $\epsilon_{\max} = 10,000$  in methanol).<sup>35, 138</sup>

The rates of hydrolysis, alcoholysis, and aminolysis of imidazolides (such as 1-acetylimidazole) are readily followed spectrophotometrically, since the azolides normally show characteristic intense absorption bands at longer wavelengths than the products.<sup>190, 191</sup>

The ultraviolet spectra of 2-imidazolones<sup>186</sup> and cyanoimidazoles<sup>186</sup> have been measured, while the spectra of aryl-substituted imidazoles, benzimidazoles and naphthimidazoles have been discussed previously.<sup>3</sup>

<sup>182</sup> G. Leandri, A. Mangini, F. Montanari, and R. Passerini, *Gazz. Chim. Ital.*, **85**, 769 (1955).

<sup>183</sup> H. Schubert and H. Baumann, *Z. Phys. Chem.* **203**, 351 (1954); *Chem. Abstr.* **49**, 5964 (1955).

<sup>184</sup> A. F. Pozharskii, *Zh. Obshch. Khim.* **34**, 630 (1964); *Chem. Abstr.* **60**, 13118 (1964).

<sup>185</sup> R. P. Saper, *Glasnik Hem. Drustva, Beograd* **25-26** (5–7), 287 (1960–1961); *Chem. Abstr.* **59**, 1196 (1963).

<sup>186</sup> R. Gompper and H. Herlinger, *Ber.* **89**, 2816 (1956).

<sup>187</sup> T. Hayashi and H. Midorikawa, *Sci. Papers Inst. Phys. Chem. Res. (Tokyo)* **58**, 139 (1964); *Chem. Abstr.* **62**, 10317 (1965).

<sup>188</sup> K. Brocklehurst and J. R. Griffiths, *Tetrahedron* **24**, 2407 (1968).

<sup>189</sup> H. Schubert and H.-D. Rudolf, *Angew. Chem. Intern. Ed. Engl.* **5**, 674 (1966).

<sup>190</sup> T. H. Fife, *J. Am. Chem. Soc.* **87**, 4597 (1965).

<sup>191</sup> H. A. Staab, *Ber.* **90**, 1320 (1957).

## F. INFRARED AND RAMAN SPECTRA

Assignments of the absorption bands of imidazole<sup>192-197</sup> in the infrared region fall into three main regions: 760–880  $\text{cm}^{-1}$  (imidazole ring), 1500–1620  $\text{cm}^{-1}$  (aromatic C–N and C–C bonds), and 2200–3600  $\text{cm}^{-1}$  (associated N–H bond). From a study<sup>196</sup> of the vibrational spectra of imidazole-1-*d*, imidazole-2,4,5-*d*<sub>3</sub>, and imidazole-*d*<sub>4</sub>, it has proved possible to assign the fundamental frequencies of imidazole in the range 30–1700  $\text{cm}^{-1}$ . In the range 1700–4000  $\text{cm}^{-1}$  stretching frequencies due to the CH groups in the 2-, 4-, and 5-positions have been distinguished.<sup>196</sup> The broad absorption band at 3200–2200  $\text{cm}^{-1}$  is attributed<sup>196</sup> to combinations and binary harmonics of internal vibrations which become intense by a Fermi-type interaction with the fundamental N–H-stretching vibration. Bands at 1680–1600 and 1585–1500  $\text{cm}^{-1}$  have been assigned to ring vibrations.<sup>193</sup>

On the basis of vibrational spectra (Raman and IR) between 4000–200  $\text{cm}^{-1}$  of 1-methylimidazole, 1-(methyl-*d*<sub>3</sub>)imidazole and 1-methylimidazole-2,4,5-*d*<sub>3</sub> in the solid, liquid, gaseous, and solution states, extensive band assignments have been made.<sup>198</sup> When a comparison was made of the spectra in different states, an interaction was postulated<sup>198</sup> between the ring C–H groups and the “pyridine” nitrogens on neighboring molecules, similar to that proposed for pyrazine.<sup>199</sup> Perchard and Novak<sup>200</sup> also examined the far-infrared spectra of imidazole, imidazole-*d*<sub>4</sub>, 1-methylimidazole, and 1-(methyl-*d*<sub>3</sub>)imidazole in the 300–33  $\text{cm}^{-1}$  range, but found no obvious correlation between hydrogen-bond frequencies and the structure of the  $\nu_{\text{N-H}}$  absorption band of crystalline imidazole.

Far-infrared data<sup>201</sup> for imidazole, pyrazole, and pyrrole in solution

<sup>192</sup> D. Garfinkel and J. T. Edsall, *J. Am. Chem. Soc.* **80**, 3807 (1958).

<sup>193</sup> P. Bassignana, C. Cogrossi, M. Gandino, and P. Merli, *Spectrochim. Acta* **21**, 605 (1965).

<sup>194</sup> C. Perchard and M.-L. Josien, *J. Chim. Phys.* **62**, 423 (1965); *Chem. Abstr.* **63**, 6474 (1965).

<sup>195</sup> C. Perchard, A. M. Bellocq, and A. Novak, *J. Chim. Phys.* **62**, 1344 (1965); *Chem. Abstr.* **64**, 16839 (1966).

<sup>196</sup> A. M. Bellocq, C. Perchard, A. Novak, and M. Josien, *J. Chim. Phys.* **62**, 1334 (1965); *Chem. Abstr.* **64**, 13560 (1966).

<sup>197</sup> Sister M. Cordes de N. D. and J. L. Walter, *Spectrochim. Acta* **24**, 237 (1968).

<sup>198</sup> C. Perchard and A. Novak, *Spectrochim. Acta A*, **23**, 1953 (1967).

<sup>199</sup> M. Ito and T. Shigeoka, *J. Chem. Phys.* **44**, 1001 (1966).

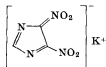
<sup>200</sup> C. Perchard and A. Novak, *J. Chem. Phys.* **48**, 3079 (1968).

<sup>201</sup> V. Lorenzelli and G. Randi, *Atti Acad. Nazl. Lincei, Rend. Classe Sci. Fis. Mat. Nat.* **36**, 646 (1964); *Chem. Abstr.* **62**, 7612 (1965).

indicates that the intermolecular hydrogen bond strengths decrease in the order: imidazole > pyrazole > pyrrole.

Zimmermann has employed infrared and Raman spectroscopy to measure the association of imidazole<sup>202</sup> and 4-methylimidazole<sup>203</sup> in nonpolar solvents.

Infrared spectra of many imidazole derivatives have been studied,<sup>204-213</sup> including aryl-substituted imidazoles,<sup>187, 209</sup> imidazolines,<sup>209</sup> cyanoimidazoles,<sup>186, 212</sup> and imidazoles which have a carbonyl function conjugated with the aromatic ring.<sup>34, 138, 210-212</sup> A close study has been made of 1-substituted and 1,2-disubstituted imidazoles,<sup>214</sup> and the position of substitution of the nitro group in 2-methyl-4(or 5)-nitroimidazole has been determined by infrared spectroscopy.<sup>215</sup> The infrared spectra of nitroimidazoles and their salts have been claimed to indicate that salt formation involves only the nitro group, with the formation of an isoimidazole ring, and in polynitroimidazoles only one nitro group is involved.<sup>216</sup>



<sup>202</sup> H. Zimmermann, *Z. Elektrochem.* **65**, 821 (1961); *Chem. Abstr.* **57**, 9230 (1962).

<sup>203</sup> H. Zimmermann, *Z. Elektrochem.* **63**, 601, 608 (1959); *Chem. Abstr.* **53**, 21023, 21163 (1959).

<sup>204</sup> D. J. Rabiger and M. M. Joullié, *J. Org. Chem.* **29**, 476 (1964).

<sup>205</sup> D. O'Sullivan, *Spectrochim. Acta* **16**, 764 (1960).

<sup>206</sup> D. J. Rabiger and M. M. Joullié, *J. Chem. Soc.* 915 (1964).

<sup>207</sup> D. O'Sullivan, *J. Chem. Soc.* 3278 (1960).

<sup>208</sup> B. K. Manukian, *Helv. Chim. Acta* **48**, 1999 (1965); *Chem. Abstr.* **64**, 4906 (1966).

<sup>209</sup> D. M. White and J. Sonnenberg, *J. Org. Chem.* **29**, 1926 (1964).

<sup>210</sup> A. M. Roe, *J. Chem. Soc.* 2195 (1963).

<sup>211</sup> W. Otting, *Ber.* **89**, 1941 (1956).

<sup>212</sup> H. A. Staab, *Ber.* **89**, 1927 (1956).

<sup>213</sup> H. A. Staab, W. Otting, and A. Ueberle, *Z. Elektrochem.* **61**, 1000 (1957); *Chem. Abstr.* **52**, 4927 (1958).

<sup>214</sup> P. Fournari, P. de Cointet, and E. Laviron, *Bull. Soc. Chim. France* 2438 (1968).

<sup>215</sup> P. Rems, F. Kajfez, and V. Sunjic, *Bull. Sci., Conseil Acad. R.S.F. Yougoslavie, Sect. A* **12**, 308 (1967).

<sup>216</sup> L. P. Epishina, V. I. Slovetskii, V. G. Osipov, O. V. Lebedev, L. I. Khmel'nitskii, V. V. Sevost'yanova, and T. S. Novikova, *Khim. Geterotsikl. Soedin.*, 716 (1967); *Chem. Abstr.* **68**, 68249 (1968).

The variation in reactivity of *N*-acetylimidazoles (and other azolides) in nucleophilic reactions involving the carbonyl group is paralleled by the marked shift in the carbonyl bands (toward higher frequencies for the more reactive compounds).<sup>212</sup> This shift, i.e., increase in the C=O force constant, can also be attributed to increased electron attraction by the heterocyclic rings.<sup>213</sup>

### G. NUCLEAR MAGNETIC RESONANCE SPECTRA

The proton magnetic resonance spectrum of imidazole shows a one-proton triplet at  $\delta = 7.64$  ppm (assigned to the 2-H) and a two-proton doublet at  $\delta = 7.01$  ppm (assigned to the 4- and 5-H). The coupling constants are  $J_{2H-5H} = J_{2H-4H} = 1.0$  Hz.<sup>217</sup> Because of rapid exchange of the N-H proton, the 4- and 5-protons become magnetically equivalent and there are no spin-spin splittings by interaction with the 1-proton.<sup>217</sup> This imino proton gives rise to a broad, distinct signal only in concentrated benzene,<sup>218</sup> acetone,<sup>218</sup> or chloroform<sup>34</sup> solutions of imidazole derivatives. The positions and halfwidths of the NH signals are very concentration dependent. With increasing concentration the signal shifts toward lower field strength with a shift ( $\delta > 10$  ppm) which is large compared with that for other hydrogen bonds.<sup>219</sup>

One of the major difficulties in obtaining NMR spectra of imidazoles is a consequence of their low solubility in most suitable solvents except for water. This may often lead to incomplete, or ill-defined, spectra, particularly where there are a number of exchangeable hydrogen atoms, e.g., in polyhydroxyalkyl-substituted imidazoles. Some imidazoles, for instance, 1-methyl- and 2-acetyl-4-methylimidazole are readily soluble in deuteriochloroform, while deuteriated pyridine, acetone, or dimethyl sulfoxide may prove useful in other cases. Reddy *et al.*<sup>220</sup> have suggested conversion of imidazoles into their *N*-acetyl derivatives which are soluble either in deuteriochloroform or in a mixture of deuteriochloroform and dimethyl sulfoxide. Although, as mentioned above, in neutral organic solvents the 4- and

<sup>217</sup> Sung Mao Wang and N. C. Li, *J. Am. Chem. Soc.* **88**, 4592 (1966).

<sup>218</sup> N. Joop and H. Zimmermann, *Z. Elektrochem.* **66**, 440 (1962); *Chem. Abstr.* **57**, 10681 (1962).

<sup>219</sup> N. Joop and H. Zimmermann, *Z. Elektrochem.* **66**, 541 (1962); *Chem. Abstr.* **57**, 13323 (1962).

<sup>220</sup> G. S. Reddy, L. Mandell, and J. H. Goldstein, *J. Chem. Soc.* 1414 (1963).

5-H atoms in imidazole have equivalent proton resonance owing to proton exchange across the N-H---N bridge, 2-methylimidazole shows some CH-NH spin splitting in concentrated sulfuric acid due to reduction in the exchange frequency.<sup>221</sup> For nitroimidazoles, 20% D<sub>2</sub>SO<sub>4</sub> has proved a satisfactory solvent.<sup>222</sup>

Barlin and Batterham<sup>223</sup> have studied the effects of solvent on chemical shifts of the anionic and cationic species of imidazoles. Protonation shifts, obtained by direct comparison of spectra in deuteriochloroform and trifluoroacetic acid, observed for 1-methylimidazoles are consistent with stabilization of the resulting cations by an amidinium-type resonance (47). Thus, for 1-methylimidazole, which



can protonate on N-3, the signal from H-2 was shifted downfield by 1.26 ppm, whereas signals from H-4 and H-5 moved only 0.52 and 0.64 ppm, respectively. This is not an unexpected phenomenon as H-2 is associated with the full positive charge, whereas H-4 and H-5 are adjacent only to part of it.

Table IV lists chemical shifts for a number of imidazoles.

Caesar and Overberger,<sup>224</sup> in a similar study with 1-methylimidazole methiodide, found that, in water as solvent, the 2-H appeared as a broad singlet at  $\delta = 8.78$  ppm, whereas the 4 (and 5)-proton signal appeared as a doublet at  $\delta = 7.53$  ppm ( $J = 1.7$  Hz in water). Protonation of the nitrogen with strong acids resulted in the aromatic protons being shifted downfield—an observation previously made by Barlin and Batterham<sup>223</sup> and Davis.<sup>225</sup> It proved possible<sup>224</sup> to split the 1-methyl signal into a doublet with a coupling constant  $J_{\text{N-CH}_2; \text{H-2}} = 0.45$  Hz, confirmation being obtained by double resonance.

On the basis of NMR spectroscopic results Staab and Mannschreck<sup>226</sup> have suggested that 4 (or 5)-substituted imidazoles exist predominantly

<sup>221</sup> H. A. Staab and A. Mannschreck, *Tetrahedron Letters* 913 (1962).

<sup>222</sup> V. Sunjic, F. Kajfez, M. Slamnik, and D. Kolbah, *Bull. Sci., Conseil Acad. R.S.F. Yougoslavie* **12**, 59 (1967); *Chem. Abstr.* **68**, 2483 (1968).

<sup>223</sup> G. B. Barlin and T. J. Batterham, *J. Chem. Soc. B* 516 (1967).

<sup>224</sup> F. Caesar and C. G. Overberger, *J. Org. Chem.* **33**, 2971 (1968).

<sup>225</sup> J. B. Davis, *Chem. Ind. (London)* 1094 (1968).

<sup>226</sup> H. A. Staab and A. Mannschreck, *Angew. Chem. Intern. Ed. Engl.* **2**, 216 (1963).

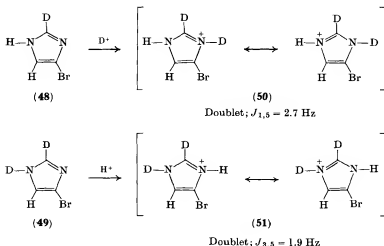
TABLE IV

CHEMICAL SHIFTS ( $\sigma$  ppm) OF AROMATIC PROTONS AND METHYL PROTONS OF SOME SIMPLE IMIDAZOLES<sup>a</sup>

Compound	Reference	2-H	4-H	5-H	1-CH <sub>3</sub>	2-CH <sub>3</sub>	4-CH <sub>3</sub>	5-CH <sub>3</sub>
Imidazole	217, 232,							
	238	7.73	7.14	7.14	—	—	—	—
1-Methylimidazole	223	7.47	7.08	6.88	3.70	—	—	—
1-Ethylimidazole <sup>b</sup>	240	7.41	6.98	6.88	—	—	—	—
2-Methylimidazole	240	—	6.96	6.96	—	2.36	—	—
4-Methylimidazole	230	7.47	—	6.81	—	—	2.23	—
4,5-Dimethylimidazole	220	7.56	—	—	—	—	2.09	2.09
1,2-Dimethylimidazole	240	—	6.79	6.73	3.52	2.30	—	—
1,4-Dimethylimidazole	240	7.20	—	6.53	3.49	—	2.15	—
1,5-Dimethylimidazole	240	7.27	6.68	—	3.42	—	—	2.10
2,4,5-Trimethylimidazole	240	—	—	—	—	2.23	1.98	1.98
4-Hydroxymethylimidazole <sup>c</sup>	35	7.87	—	7.07	—	—	—	—
2-Bromo-1-methylimidazole	223	—	7.04	7.04	3.64	—	—	—
2-Bromo-1-methyl-4-nitroimidazole	223	—	—	7.91	3.80	—	—	—
5-Bromo-1-methylimidazole	223	7.59	7.07	—	3.63	—	—	—
5-Bromo-1-methyl-4-nitroimidazole	223	7.68	—	—	3.79	—	—	—
1-Methyl-4-nitroimidazole	223	7.54	—	7.87	3.90	—	—	—
1-Methyl-5-nitroimidazole	223	7.64	8.09	—	4.05	—	—	—
4-Iodo-5-methylimidazole	230	7.27	—	—	—	—	—	—
4-Iodoimidazole	230	7.43	—	7.02	—	—	—	—
4-Bromoimidazole	230	7.33	—	6.91	—	—	—	—
4,5-Diiodoimidazole	230	7.47	—	—	—	—	—	—
4,5-Dibromoimidazole	230	7.35	—	—	—	—	—	—

<sup>a</sup> Solvents not specified.<sup>b</sup> CH<sub>3</sub>-CH<sub>2</sub>-; triplet 1.36, quartet 3.91 ppm.<sup>c</sup> 4-CH<sub>2</sub>OH, 4.55 ppm.

in one form, for which distinction can be made on the basis of the respective spin-spin coupling constants. When 4(or 5)-bromo-2-deuterioimidazole (48) was dissolved in concentrated  $D_2SO_4$  a doublet with  $J = 2.7$  Hz was observed for the 4(or 5)-resonance of the imidazole cation as a result of coupling with the 1-H. The doublet could be converted into a singlet by exchange of the 1-H for deuterium. On the other hand, in concentrated sulfuric acid, 1,2-dideuterio-4(or 5)-bromoimidazole (49) showed a different doublet with  $J = 1.9$  Hz. Deuterium-hydrogen exchange converted this into the pair of doublets previously reported<sup>221</sup> for the 2-deuterio-4(or 5)-bromimidazolium cation in sulfuric acid. It was concluded<sup>226</sup> that 2-deuterio-4(or 5)-bromoimidazole in  $D_2SO_4$  and the corresponding 1,2-dideuterio compound in  $H_2SO_4$  give two different cations (50 and 51, respectively), and that under these conditions exchange with the solvent is slow.



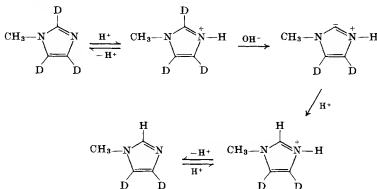
The assignment of these structures was based on the assumption (valid for such five-membered ring systems) that the greater coupling constant corresponds to the cation (50) in which the interacting protons are adjacent. These results suggest that the imidazoles (48) and (49) exist as the 4-substituted isomers.

The use of NMR spectroscopy permitted the observation<sup>226a</sup> that

<sup>226a</sup> T. M. Harris and J. C. Randall, *Chem. Ind. (London)* 1728 (1965).



deuterium exchange at the 2-position of imidazoles can occur either in the presence or absence of added base. The proposed exchange mechanism is:



Nuclear magnetic resonance spectroscopy has been used to determine product ratios from photoisomerization reactions of 1,4,5-trimethylimidazole,<sup>227</sup> to determine substituent positions,<sup>228-231</sup> and, in general, to study structural problems.<sup>123, 124, 138-139, 217, 231-240</sup> Studies of NMR spectra of the halogenation products of imidazoles show that the 4-halogenated compound is formed initially.<sup>230</sup>

<sup>227</sup> P. Beak, J. L. Miesel, and W. R. Messer, *Tetrahedron Letters* 5315 (1967).

<sup>228</sup> J. S. G. Cox, C. Fitzmaurice, A. R. Katritzky, and G. J. T. Tiddy, *J. Chem. Soc. B* 1251 (1967).

<sup>229</sup> F. Kajfez, D. Kolbah, M. Oktobdzija, T. Fajdiga, M. Stannik, and V. Sunjic, *Croat. Chem. Acta* **39**, 199 (1967); *Chem. Abstr.* **68**, 49513 (1968).

<sup>230</sup> P. M. S. R. Naidu and H. B. Benusan, *J. Org. Chem.* **33**, 1307 (1968).

<sup>231</sup> L. Fowden, F. F. Noe, J. H. Ridd, and R. F. M. White, *Proc. Chem. Soc.* 131 (1959).

<sup>232</sup> A. Mannschreck, W. Seitz and H. A. Staab, *Ber. Bunsenges. Physik. Chem.* **67**, 470 (1963); *Chem. Abstr.* **59**, 4703 (1963).

<sup>233</sup> K. Tori and T. Nakagawa, *J. Phys. Chem.* **68**, 3163 (1964).

<sup>234</sup> N. Joop and H. Zimmermann, *Z. Phys. Chem.* **42**, 61 (1964); *Chem. Abstr.* **61**, 14058 (1964).

<sup>235</sup> E. O. Bishop and R. E. Richards, *Biochem. J.* **86**, 277 (1963).

<sup>236</sup> H. B. Benusan and P. M. S. R. Naidu, *Biochemistry* **6**, 12 (1967).

<sup>237</sup> C. T. Holloway, R. P. M. Bond, I. G. Knight, and R. B. Beechey, *Biochemistry* **6**, 19 (1967).

<sup>238</sup> D. M. W. Anderson, J. L. Duncan, and F. J. C. Rossotti, *J. Chem. Soc.* 2165 (1961).

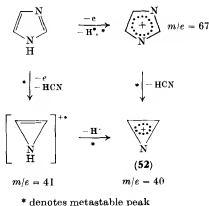
<sup>239</sup> R. M. Hoskinson, *Australian J. Chem.* **21**, 1913 (1968).

<sup>240</sup> P. D. Wethy, C. G. Begg, and M. R. Grimmett, unpublished work.

Carbon-13 magnetic resonance studies have been made on imidazole and its corresponding anion and cation.<sup>241-243</sup> Linear relationships have been found<sup>243</sup> between the <sup>13</sup>C and proton chemical shifts and the Hückel  $\pi$ -electron densities in diazoles and triazoles.

### H. MASS SPECTROMETRY

Apart from investigations of imidazolyl quinoline alkaloids<sup>244, 245</sup> and purines,<sup>246</sup> the mass spectra of simple imidazoles were not studied until very recently.<sup>247-249</sup> The spectra exhibit pronounced molecular ions and characteristic fragmentation patterns, while skeletal rearrangements are rare. One of the major fragments in the mass spectrum is the azirinium cation (52) at  $m/e$  40.<sup>246</sup>



<sup>241</sup> R. J. Pugmire and D. M. Grant, *J. Am. Chem. Soc.* **90**, 4232 (1968).

<sup>242</sup> F. J. Weigert and J. D. Roberts, *J. Am. Chem. Soc.* **90**, 3543 (1968).

<sup>243</sup> B. M. Lynch, *Chem. Commun.* 1337 (1968).

<sup>244</sup> V. P. Joynt, R. R. Arndt, A. Jordaan, K. Biemann, and J. L. Occolowitz, *J. Chem. Soc. B* 980 (1966).

<sup>245</sup> G. Spiteller and M. Spiteller-Friedmann, *Monatsh.* **94**, 742 (1963); *Chem. Abstr.* **59**, 12281 (1963).

<sup>246</sup> G. Spiteller and M. Spiteller-Friedmann, *Monatsh.* **93**, 632 (1962); *Chem. Abstr.* **58**, 1018 (1963).

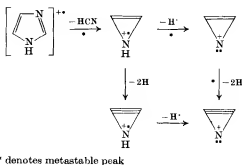
<sup>247</sup> J. H. Bowie, R. G. Cooks, S.-O. Lawesson, and G. Schroll, *Australian J. Chem.* **20**, 1613 (1967).

<sup>248</sup> R. Hodges and M. R. Grimmett, *Australian J. Chem.* **21**, 1085 (1968).

<sup>249</sup> J. H. Bowie, P. F. Donaghue, H. J. Rodda, and B. K. Simons, *Tetrahedron* **24**, 3965 (1968).

Deuterium-labeling experiments show that HCN is lost from the imidazole molecular ion by a nonspecific process,<sup>247</sup> but the substitution pattern of imidazole greatly affects the loss of HCN which may come from the 2,3-positions (1- and 4-methylimidazole), or the 1,5- or 3,4-positions (2-methylimidazole). The observation that 1,2-dimethyl- and 1-methyl-2-mercaptoimidazole show negligible loss of HCN from the molecular ions suggests that HCN is not readily lost from the 3,4-position.<sup>247</sup>

At energies above the range 17–26 eV the azirinium cation further loses a hydrogen molecule giving  $C_2N^+$ , possibly by the following pathway<sup>248</sup>:



Only four imidazole compounds have been found to undergo skeletal rearrangements.<sup>247, 249</sup>

It appears that mass spectrometry is of considerable value in structure determination although, at present, it is not possible to differentiate between 2- and 4-substituted isomers. The technique has been used to establish the structure of 4-(imidazol-4-yl)butane-1,2,3-triol<sup>55</sup> which, unlike most carbohydrate derivatives, shows a molecular ion. The mass spectra of 2-alkylbenzimidazoles<sup>246</sup> and mercaptoimidazoles<sup>124</sup> have been examined, while use has been made of mass spectrometry in the identification of some alkyl, aryl, and acyl imidazoles.<sup>138</sup>

## I. ELECTRON SPIN RESONANCE

The ESR spectrum of  $\gamma$ -irradiated imidazole<sup>250</sup> shows that the primary radical is due to removal of the imino hydrogen atom, and

<sup>250</sup> B. Lamotte and P. Servoz-Gavin, *Proc. Tihany Symp. Radiat. Chem.*, 2nd, Tihany, Hungary 233 (1966); *Chem. Abstr.* **67**, 59592 (1967).

the secondary radical is a  $\pi$ -electron radical, with the  $\pi$ -orbitals being on the two nitrogens and on C-4 and C-5. Electron proton resonance spectra of copper(II) complexes of imidazole have been examined.<sup>251</sup> The photochromic decay reaction of hexaphenylbiimidazolyl has been studied using ultraviolet and ESR spectrometry.<sup>252</sup>

### J. OPTICAL ROTATORY DISPERSION AND POLAROGRAPHY

The rotatory dispersion of polyhydroxyalkyl-substituted benzimidazoles has been studied.<sup>253</sup>

Polarographic data has been obtained for imidazole-4-aldehyde<sup>254</sup> and for 1-methyl- and 1-benzylimidazole-2-aldehyde.<sup>214</sup> The polarographic behavior was found to resemble pyridine compounds more than pyrroles.

### K. CHROMATOGRAPHY

Since Huebner,<sup>255</sup> Ames and Mitchell,<sup>256</sup> and Cowgill<sup>257</sup> made the initial studies of the paper chromatography of imidazoles, there have been rapid advances in this field.

The compounds are generally identified on chromatograms with diazotized sulfanilic acid (modified Pauly reagent<sup>258</sup>) which is capable of detecting as little as 0.1  $\mu$ g of an imidazole which does not have a substituted imino nitrogen or a carboxyalkyl substituent, and which has at least one unsubstituted ring carbon atom. Instead of the usual red or orange colors, yellow dyes are reported<sup>255</sup> to be often characteristic of 2-substituted imidazoles. Iodine in chloroform or carbon tetrachloride may also be used to produce transient brown or yellow spots on chromatograms. This iodine reagent is generally successful with imidazoles which fail to react with Pauly reagent. Nitroimidazoles on chromatograms are first reduced to the corresponding aminoimidazoles by spraying with 1.5%  $\text{TiCl}_3$  in 10% acetic acid,<sup>259</sup> when the

<sup>251</sup> A. T. Nikitaev and K. I. Zamaraev, *Zh. Strukt. Khim.* **8**, 429 (1967); *Chem. Abstr.* **67**, 77785 (1967).

<sup>252</sup> M. A. J. Wilks and M. R. Willis, *J. Chem. Soc. B* 1526 (1968).

<sup>253</sup> W. S. Chilton and R. C. Krahn, *J. Am. Chem. Soc.* **90**, 1318 (1968).

<sup>254</sup> E. Laviron, *Bull. Soc. Chim. France* **2325** (1961); **2840** (1963).

<sup>255</sup> C. F. Huebner, *J. Am. Chem. Soc.* **73**, 4667 (1951).

<sup>256</sup> B. N. Ames and H. K. Mitchell, *J. Am. Chem. Soc.* **74**, 252 (1952).

<sup>257</sup> R. W. Cowgill, *Anal. Chem.* **27**, 1519 (1955).

<sup>258</sup> H. Pauly, *Z. Physiol. Chem.* **42**, 508 (1904).

<sup>259</sup> J. E. Stambaugh and R. W. Manthei, *J. Chromatog.* **31**, 128 (1967).

aminoimidazoles can be detected with diazotized sulfanilic acid, *p*-dimethylaminobenzaldehyde, or ninhydrin. Ceric sulfate and potassium iodoplatinate have also been employed as detecting agents.<sup>139</sup>

Recent data relating to the paper chromatography of imidazoles can be found in the work of Komoto,<sup>260</sup> Smith,<sup>261,262</sup> Robinson and Shepherd,<sup>263</sup> Grimmett,<sup>264</sup> Middleton,<sup>265</sup> Khattak *et al.*,<sup>266</sup> Inoue,<sup>267</sup> Arient and Marhan,<sup>268</sup> Neufeld and Chayen,<sup>269</sup> and Rousseau *et al.*<sup>270</sup> It has been noted<sup>260</sup> that  $R_f$  values of imidazoles increase with increasing basic strength of the compounds. The use of  $R_{Im}$  values [where  $R_{Im}$  = ratio of distance traveled by compound to distance traveled by the parent base (imidazole)] is preferable to  $R_f$  values which require very strict control of conditions for any adequate degree of reproducibility.<sup>264,271,272</sup>

Thin-layer chromatography on alumina,<sup>271</sup> silica gel,<sup>139,271,272</sup> cellulose,<sup>262,272</sup> Avicel,<sup>259,262</sup> and polyamide<sup>273</sup> thin layers has extended considerably the applications of chromatography to the separation and purification of imidazoles. Polyamide layers are useful especially for the separation of imidazoles and their 1-methyl derivatives and (using methyl ethyl ketone as solvent) allows separation of the more polar compounds such as 1,3-dimethylimidazolium iodide.<sup>273</sup> Imidazolines have also been separated by thin-layer chromatography.<sup>274</sup>

<sup>260</sup> M. Komoto, *J. Agr. Chem. Soc., Japan* **36**, 541 (1962); *Chem. Abstr.* **60**, 2332 (1964).

<sup>261</sup> I. Smith, "Chromatographic Techniques," Heinemann, London, 1958.

<sup>262</sup> I. Smith, L. J. Rider, and R. P. Lerner, *J. Chromatog.* **26**, 449 (1967).

<sup>263</sup> B. Robinson and D. Shepherd, *J. Pharm. Pharmacol.* **13**, 374 (1961).

<sup>264</sup> M. R. Grimmett, Ph.D. Thesis, Massey Univ., New Zealand (1965).

<sup>265</sup> J. E. Middleton, *J. Clin. Pathol.* **18**, 605 (1965); *Chem. Abstr.* **64**, 995 (1966).

<sup>266</sup> M. N. Khattak, N. T. Barker, and J. H. Green, *Analyst* **91**, 526 (1966).

<sup>267</sup> M. Inoue, *Nagasaki Igakkai Zasshi* **28**, 1283 (1953); *Chem. Abstr.* **48**, 7088 (1954).

<sup>268</sup> J. Arient and J. Marhan, *J. Chromatog.* **6**, D16 (1961).

<sup>269</sup> E. Neufeld and R. Chayen, *J. Chromatog.* **35**, 445 (1968).

<sup>270</sup> R. J. Rousseau, R. K. Robins, and L. B. Townsend, *J. Chromatog.* **38**, D106 (1968).

<sup>271</sup> M. R. Grimmett and E. L. Richards, *J. Chromatog.* **18**, 605 (1965).

<sup>272</sup> M. R. Grimmett and E. L. Richards, *J. Chromatog.* **20**, 171 (1965).

<sup>273</sup> A. Verweij, *J. Chromatog.* **24**, 473 (1966).

<sup>274</sup> S. Goenechea, *J. Chromatog.* **36**, 375 (1968).

Column chromatography on cellulose<sup>34, 45, 47, 53</sup> (and as a Chromax column<sup>55</sup>), alumina,<sup>34</sup> and ion-exchange resins<sup>34, 53, 55, 275</sup> has allowed separation of larger quantities. It would be useful to be able to separate imidazoles by gas chromatography, but as yet there has been little work reported in this field, although Boon and Sudds<sup>276</sup> used the technique to separate imidazolines. Tham and Holmstedt<sup>276a</sup> used gas chromatography to examine histamine metabolites, and it has also been employed recently in studies of histidine,<sup>276b</sup> and 1-substituted imidazoles.<sup>276c</sup>

Allied with the chromatography of imidazoles have been methods of estimation of the compounds, particularly those of biological importance, either on the chromatograms or after elution. Most workers have used diazotized aromatic amines as colorimetric reagents,<sup>53, 277-285</sup> particularly nonsulfonated diazotized aniline derivatives.<sup>281-285</sup> Mosebach *et al.*<sup>286</sup> initially hydrolyzed *N*-substituted imidazoles with 10 *N* hydrochloric acid before separating the compounds by ion-exchange and paper chromatographic techniques prior to estimation. A number of other methods exist for the colori-

<sup>275</sup> S. K. Ganguly and H. Bhattacharya, *Ind. J. Pharm.* **16**, 72 (1954); *Chem. Abstr.* **49**, 417 (1955).

<sup>276</sup> P. F. G. Boon and W. Sudds, *J. Pharm. Pharmacol., Suppl.* **19**, 88 (1967).

<sup>276a</sup> R. Tham and B. Holmstedt, *J. Chromatog.* **19**, 286 (1965).

<sup>276b</sup> D. Roach, C. W. Gehrke, and R. W. Zumwalt, *J. Chromatog.* **43**, 311 (1969).

<sup>276c</sup> P. Beak and W. Messer, *Tetrahedron* **25**, 3287 (1969).

<sup>277</sup> G. Barac, *Bull. Soc. Chim. Biol.* **32**, 287 (1950); *Chem. Abstr.* **44**, 9501 (1950).

<sup>278</sup> E. Havinga, L. Seekles, and T. H. Strengers, *Rec. Trav. Chim.* **66**, 605 (1947); *Chem. Abstr.* **42**, 2309 (1948).

<sup>279</sup> E. P. Stepanyan, *Klin. Med. (USSR)* **32**, 42 (1954); *Chem. Abstr.* **49**, 5562 (1955).

<sup>280</sup> H. Frank and H. Petersen, *Z. Physiol. Chem.* **299**, 1 (1955).

<sup>281</sup> J. Barraud, L. Genevois, and G. Ringenbach, *Compt. Rend.* **222**, 760 (1946).

<sup>282</sup> M. Loeper, A. Lesure, and M. Mougeot, *Compt. Rend. Soc. Biol.* **119**, 173 (1935).

<sup>283</sup> M. Pesetz and P. Poirier, *Bull. Soc. Chim. France* 754 (1953).

<sup>284</sup> T. Ito and Y. Wada, *Nippon Univ. J. Med.* **1**, 353 (1959); *Chem. Abstr.* **56**, 11996 (1962).

<sup>285</sup> T. A. Goryukhina, *Ukr. Biokhim. Zh.* **31**, 138 (1959); *Chem. Abstr.* **54**, 3575 (1960).

<sup>286</sup> K. O. Mosebach, G. Rieck, S. Beck, and R. Schneider, *Z. Physiol. Chem.* **348**, 620 (1967); *Chem. Abstr.* **67**, 80332 (1967).

metric estimation of histamine and histidine.<sup>287-289</sup> A potentiometric assay method for histamine hydrochloride using sodium tetraphenylborate has been reported.<sup>290</sup>

### L. THERMODYNAMIC DATA

The enthalpy of formation of crystalline imidazole is  $14.6 \pm 0.8$  kcal mole<sup>-1</sup>; its heat of sublimation is  $16.0 \pm 1.0$  kcal mole<sup>-1</sup>, and the heat of formation of gaseous imidazole is  $30.6 \pm 1.8$  kcal mole<sup>-1</sup>.<sup>291</sup> From these data the resonance energy of imidazole has been calculated as 14.2 kcal mole<sup>-1</sup>.<sup>291, 292</sup> From an infrared examination of the association of 4-methylimidazole in carbon tetrachloride and in 1,1,2,2-tetrachloroethane,<sup>293</sup> the concentration dependence of the maximum extinction coefficient of the free NH valency band allowed determination of the monomer content, the mean viscosity, and the equilibrium constants  $K_{12}$  and  $K_{13}$ . From the temperature dependence of these values the mean heat of addition ( $8.2 \pm 0.5$  kcal mole<sup>-1</sup>) and the heats of formation of the dimers and trimers (10.2 and 8.1 kcal mole<sup>-1</sup>, respectively) were obtained. Although the mean heat of addition was found to be about 3 kcal mole<sup>-1</sup> higher than that of Zimmermann<sup>293</sup> this is not contradictory to the assumption that the imidazoles form chainlike associations with angled structures.

### M. QUANTUM MECHANICAL CALCULATIONS

The contradictory nature of the  $\pi$ -electron density values at various positions in the imidazole molecule has been commented on by Pozharskii *et al.*<sup>3</sup>

Calculations by Brown and Heffernan,<sup>294</sup> based on the self-consistent

<sup>287</sup> R. W. Cowgill, *Anal. Chem.* **27**, 1521 (1955).

<sup>288</sup> P. M. Newman and J. H. Turnbull, *Biochem. J.* **74**, 379 (1960).

<sup>289</sup> R. Kapeller-Adler, *Biochem. Z.* **206**, 271 (1934); *Chem. Abstr.* **28**, 5487 (1934).

<sup>290</sup> T. Espersen, *Dansk. Tidsskr. Farm.* **33**, 113 (1959); *Chem. Abstr.* **53**, 22735 (1959).

<sup>291</sup> A. F. Bedford, P. B. Edmondson, and C. T. Mortimer, *J. Chem. Soc.* 2927 (1962).

<sup>292</sup> H. Zimmermann and H. Giesenfelder, *Z. Elektrochem.* **65**, 368 (1961); *Chem. Abstr.* **55**, 21783 (1961).

<sup>293</sup> G. Geisler, J. Fruwert, and A. Kuennecke, *Z. Physik. Chem.* **41**, 49 (1964); *Chem. Abstr.* **61**, 6892 (1964).

<sup>294</sup> R. D. Brown and M. L. Heffernan, *Australian J. Chem.* **12**, 543 (1959).

field theory method (LCAO-SCF) which takes into account the difference between the two nitrogen atoms, and by Hamano and Hamaka,<sup>295</sup> suggest that in the neutral molecule the electron density at C-4 (or C-5) is greater than at C-2, and that in the corresponding imidazole cation and anion the electron density is higher at C-2.<sup>294</sup> Recent calculations by Adam and Grimison<sup>296</sup> of sigma-complex energies and total electron densities of the imidazole cation, anion, and neutral molecule, indicate that where electrophilic substitution is believed to involve a sigma complex, good agreement is obtained with the experimentally observed site of substitution. In this and a subsequent publication<sup>297</sup> the extended Hückel theory electron densities were calculated for the 2- and 4-positions of the imidazole cation, neutral molecule, and anion (see Table V).

TABLE V  
CALCULATED EHT ELECTRON DENSITIES<sup>a</sup>

Ring position	Imidazole cation	Imidazole neutral molecule	Imidazole anion
2	$\sigma = 2.62$	$\sigma = 2.60$	$\sigma = 2.57$
	$\pi = 0.833$	$\pi = 0.833$	$\pi = 0.833$
	$\sigma + \pi = 3.45$	$\sigma + \pi = 3.43$	$\sigma + \pi = 3.40$
4	$\sigma = 2.82$	$\sigma = 2.81$	$\sigma = 2.80$
	$\pi = 1.06$	$\pi = 1.06$	$\pi = 1.06$
	$\sigma + \pi = 3.88$	$\sigma + \pi = 3.87$	$\sigma + \pi = 3.86$

<sup>a</sup> W. Adam and A. Grimison, *Tetrahedron* **22**, 835 (1966); W. Adam, A. Grimison, and G. Rodriguez, *Tetrahedron* **23**, 2513 (1967).

Extended Hückel theory calculations also suggest significant polarization of the sigma framework<sup>298</sup> in which the sigma polarization appears to follow simple electro-negativity considerations. The calculated  $\pi$  polarizations are independent of, and may be opposed to, the corresponding sigma polarizations. Good correlation was observed<sup>243, 298</sup> between the total ( $\sigma + \pi$ ) calculated electron densities and the experimental proton and <sup>13</sup>C chemical shifts.

<sup>295</sup> H. Hamano and M. Hamaka, *Tetrahedron* **18**, 985 (1962).

<sup>296</sup> W. Adam and A. Grimison, *Tetrahedron* **22**, 835 (1966).

<sup>297</sup> W. Adam, A. Grimison, and G. Rodriguez, *Tetrahedron* **23**, 2513 (1967).

<sup>298</sup> W. Adam and A. Grimison, *Theoret. Chim. Acta* **7**, 342 (1967).



The generalized free electron molecular orbital method (G-FEMO) gives a good description of the ground state properties of imidazole and yields equivalent results<sup>299</sup> to Hückel molecular orbital calculations.

Calculations (LCAO-SCF) of  $\pi$  energies of protonation of the free base show that the electronic effect of methyl substituents is wholly inductive.<sup>300</sup> Gelus *et al.*<sup>301</sup> have calculated electronic structures for imidazole and benzimidazole (using the LCAO-SCF method), taking into account both  $\sigma$  and  $\pi$  electrons. The energies of bonds between hydrogen atoms and the hetero ring were calculated, and, by approximation, this information was used to explain changes in stability noted in pyrolysis experiments. The same workers<sup>302</sup> have correlated thermal stabilities of imidazoles with resonance energies, and, in particular, with the energies of the highest filled molecular orbitals.

## IV. Chemical Properties

### A. STRUCTURE

The classical imidazole structure (53) is not consistent with the aromatic behavior, tautomerism, and high dipole moment of the



molecule. A saltlike structure (54) for imidazoles was proposed by Efros<sup>303</sup> and Otting,<sup>304</sup> but this is not supported by evidence obtained by Zimmermann from X-ray diffraction analysis,<sup>181</sup> spectroscopy,<sup>203, 219</sup> acid-base equilibria,<sup>219</sup> and measurements of association energy, mesomerism, and dipole moments.<sup>202</sup> Although the dipole moment indicates polarization toward the 2:3-bond, this polarization is not

<sup>299</sup> W. Woznicki and B. Zurawski, *Acta Phys. Pol.* **31**, 95 (1967); *Chem. Abstr.* **67**, 90327 (1967).

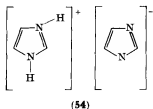
<sup>300</sup> J. D. Vaughan, D. C. Fullerton, and Chin-An Chang, *Intern. J. Quantum Chem.* **2**, 205 (1968).

<sup>301</sup> M. Gelus, P. M. Vay, and G. Berthier, *Theoret. Chim. Acta* **9**, 182 (1967).

<sup>302</sup> M. Gelus and J. M. Bonnier, *J. Chim. Phys.* **65**, 253 (1968).

<sup>303</sup> L. S. Efros and B. A. Porai-Koshits, *Zh. Obshch. Khim.* **23**, 697 (1953); *Chem. Abstr.* **48**, 7603 (1954).

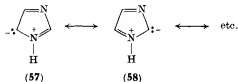
<sup>304</sup> W. Otting, *Chem. Ber.* **89**, 2887 (1956).



great enough for an ionic structure (54) or a dipolar structure (55). Rather, a mesomeric structure represented by (56) or a set of resonance



structures in which dipolar structures such as (57) and (58) are contributors, would appear to give the most accurate picture of the molecule.

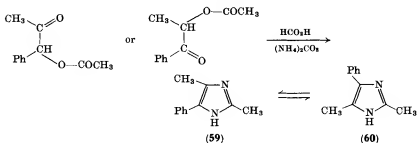


It is not possible to separate the isomers of imidazole in which the 4- or 5-positions are substituted (and the imino nitrogen is unsubstituted), although, as mentioned previously (Section III, G), they are reported to enter into chemical reactions in one of the tautomeric forms.<sup>226, 305</sup> Exchange of the imino hydrogen atom across the N-H--N bridge between molecules in neutral organic solvents would appear to explain the tautomeric behavior.<sup>221</sup> The cations and anions of both isomers are also equivalent. Recent calculations<sup>306</sup> of intermediate tunnel frequencies in the bridge bond of imidazole show that there is rapid proton exchange in the ground state ( $\nu_t$   $10^{-9}$  sec $^{-1}$ ),

<sup>305</sup> J. H. Ridd and B. V. Smith, *J. Chem. Soc.* 1363 (1960).

<sup>306</sup> J. Brickmann and H. Zimmermann, *Ber. Bunsenges. Physik. Chem.* **70**, 521 (1966); *Chem. Abstr.* **65**, 6321 (1966).

and the first excited state of the NH valence vibration has  $\nu_t$   $10^{10}$   $\text{sec}^{-1}$ . Further proof of the tautomerism comes from numerous synthetic experiments; as one example, the equivalent compounds 2,4-dimethyl-5-phenylimidazole (**59**) and 2,5-dimethyl-4-phenylimidazole (**60**) have been prepared from isomeric acyloxyketones.<sup>307</sup>



Association of compounds containing the imidazole ring with an unsubstituted NH group is best explained by formation of intermolecular hydrogen bonds.<sup>167, 163, 179, 205, 218, 293, 308</sup>

## B. AROMATIC CHARACTER AND REACTIVITY

The contributions of "ionic" resonance structures of imidazole are more important than the contribution of "ionic" structures to benzene. Because of this the imidazole ring possesses increased reactivity. Electrophilic reagents attack lone electron pairs on the multiply bonded nitrogen atom, but not at the imino nitrogen. The carbon atoms of the ring are attacked by electrophilic, nucleophilic, and free radical reagents, although there are few references<sup>309, 310</sup> to the latter reaction type. Imidazole has a high degree of aromatic character<sup>291, 292</sup> and is very stable with respect to oxidation and hydrogenation. In fact, oxidation of benzimidazole with permanganate, dichromate,<sup>147, 149</sup> or

<sup>307</sup> A. Novelli and A. de Santis, *Biol. Soc. Quim., Peru* **33**, 111 (1967); *Chem. Abstr.* **69**, 36032 (1968).

<sup>308</sup> A. N. Nesmeyanov, D. N. Kravstov, A. P. Zhukov, P. M. Kochergin, and G. K. Semin, *Dokl. Akad. Nauk SSSR* **179**, 102 (1968); *Chem. Abstr.* **69**, 82162 (1968).

<sup>309</sup> W. Langenbeck, *J. Prakt. Chem.* **119**, 77 (1928); *Chem. Abstr.* **22**, 2356 (1928).

<sup>310</sup> W. Treibs, *Naturwissenschaften* **49**, 13 (1962); *Chem. Abstr.* **57**, 9840 (1962).

hydrogen peroxide<sup>148</sup> results in oxidation of the benzene ring. Catalytic reduction of aryl- and furylimidazoles<sup>311-314</sup> results in reduction of the aryl and furyl rings. 2-Methyl-4,5-diphenylimidazole, however, forms the imidazolidine when reduced over a palladium catalyst.<sup>315</sup> Reaction of *N*-bromosuccinimide with imidazole (or its 4-substituted derivatives) in aqueous medium leads to oxidative degradation of the ring, yielding as products ammonia, glyoxal (or the corresponding substituted glyoxal), and (presumably) formamide.<sup>316</sup> The thermal stabilities of a number of imidazole derivatives, determined by pyrolysis experiments, confirm the great stability of the imidazole ring, e.g., pyrolysis temperature of imidazole, 590°C; benzimidazole, 405°C.<sup>302</sup>

There has been considerable study of the aromatic substitution reactions undergone by the imidazole ring and major advances have been made in recent years to bring us closer to an understanding of some of the apparently anomalous reactions which occur. The courses of many reactions are profoundly affected by the reaction conditions which determine whether imidazole reacts as the conjugate acid, neutral molecule, or conjugate base. Total electron density calculations (Section III, M) predict that electrophilic attack should occur preferentially at carbon-4. Thus nitration of the imidazolium cation in sulfuric acid solution<sup>317</sup> yields 4-nitroimidazole. Iodination also occurs initially at carbon-4,<sup>318</sup> eventually forming 2,4,5-triiodoimidazole. On the other hand, diazo coupling occurs initially at position 2,<sup>319</sup> and therefore it is evident that the substitution reactions are more complex than present theoretical considerations would predict.

<sup>311</sup> H. Schubert, E. Hagen, and G. Lehmann, *J. Prakt. Chem.* **17**, 173 (1962); *Chem. Abstr.* **58**, 2445 (1963).

<sup>312</sup> H. Schubert and L. Selisko, *J. Prakt. Chem.* **16**, 1 (1962); *Chem. Abstr.* **58**, 1329 (1963).

<sup>313</sup> H. Schubert and S. Hofmann, *J. Prakt. Chem.* **7**, 119 (1958); *Chem. Abstr.* **53**, 15061 (1959).

<sup>314</sup> H. Schubert and H. Fritsche, *J. Prakt. Chem.* **7**, 207 (1958); *Chem. Abstr.* **53**, 15062 (1959).

<sup>315</sup> R. S. Hanlick and W. F. Bruce, U.S. Patent 2,750,379 (1956); *Chem. Abstr.* **51**, 2054 (1957).

<sup>316</sup> G. L. Schmir and L. A. Cohen, *Biochemistry* **4**, 533 (1965).

<sup>317</sup> M. W. Austin, J. R. Blackborow, J. H. Ridd, and B. V. Smith, *J. Chem. Soc.* 1051 (1965).

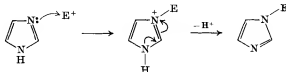
<sup>318</sup> A. Grimison and J. H. Ridd, *Proc. Chem. Soc.* 256 (1958).

<sup>319</sup> R. G. Fargher and F. L. Pyman, *J. Chem. Soc.* 217 (1919).

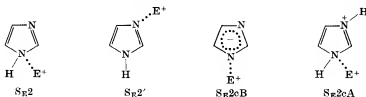
## C. ELECTROPHILIC SUBSTITUTION REACTIONS

## 1. At the Multiply Bonded Ring Nitrogen

Electrophilic attack at the tertiary nitrogen is followed by loss of a proton from the imino nitrogen when the imidazole has a free NH



group. Tautomerism in imidazoles is a special case of this reaction where the electrophilic reagent is a proton (or another imidazole molecule). The same class of reaction is involved in the imidazole-catalyzed hydrolysis of esters in biological systems.<sup>320, 321</sup> Unprotonated imidazole is believed to act as the nucleophilic catalyst.<sup>321</sup> It should be noted, as mentioned by Pozharskii *et al.*,<sup>3</sup> that the reaction is not a simple one, because, depending on the reaction conditions, imidazole can react as the neutral molecule ( $S_E2$  and  $S_E2'$  mechanisms), the conjugate base ( $S_E2cB$  mechanism), or as the conjugate acid ( $S_E2cA$  mechanism). Substituents on the imidazole ring affect the



electron density at the tertiary nitrogen and so alter the  $pK_a$  value of the compound, resulting in either an increase or decrease in the ease of electrophilic substitution.

a. *Salt Formation with Acids.* Because they readily form crystalline salts with a variety of acids, imidazoles are often isolated and purified as the oxalates, nitrates, hydrochlorides, picrates, chloroplatinates, etc. The formation of crystalline salts of polyhydroxyalkylimidazoles with sodium tetraphenylborate has been employed by Komoto.<sup>45</sup>

<sup>320</sup> J. B. Milstien and T. H. Fife, *J. Am. Chem. Soc.* **96**, 2164 (1968).

<sup>321</sup> R. W. Hay and R. J. Trethewey, *Australian J. Chem.* **21**, 109 (1969).

Hydrogen bonding between imidazole molecules to give associations containing 5–20 imidazole nuclei may be regarded as a similar reaction, although the bulk of experimental evidence does not support the saltlike structures proposed by Otting.<sup>304</sup>

b. *Reaction with Metal Ions.* Complexes form readily when imidazoles act as ligands with such cations as  $\text{Co}^{2+}$ ,<sup>322–324</sup>  $\text{Cu}^{2+}$ ,<sup>323–326</sup>  $\text{Cd}^{2+}$ ,<sup>326</sup>  $\text{Hg}^{2+}$ ,<sup>327</sup>  $\text{Ni}^{2+}$ ,<sup>323, 324, 328</sup> and  $\text{Zn}^{2+}$ .<sup>322, 329, 330</sup> With  $\text{Cu}^{2+}$  and  $\text{Zn}^{2+}$  the coordination number is 4<sup>331</sup> or 6,<sup>330</sup> with  $\text{Ni}^{2+}$  it is 6,<sup>328</sup> and with  $\text{Hg}^{2+}$  the value is 2.<sup>327</sup> Coordination polymers of imidazole and various iron carbonyls have been studied,<sup>332</sup> as have the reactions of hemoglobins<sup>333</sup> and niobium oxychloride<sup>334</sup> with imidazoles.

The literature dealing with imidazole complexes has increased rapidly in recent years, to such an extent that anything more than a cursory survey is outside the scope of the present review.

c. *Alkylation of Imidazoles.* The most satisfactory yields of 1-alkylimidazoles are obtained when the alkylation is carried out in the presence of alkaline reagents. Under these conditions the conjugate base of the imidazole is alkylated, and the increased nucleophilic character of the ring nitrogen atoms in the anion allow the alkylation to take place at temperatures low enough to avoid formation of large amounts of the (dialkylated) quaternary salts. Thus, the reaction of

<sup>322</sup> J. Schubert, E. L. Lind, W. M. Westfall, R. Pfeleger, and N. C. Li, *J. Am. Chem. Soc.* **80**, 4799 (1958).

<sup>323</sup> W. J. Eilbeck, F. Holmes, C. E. Taylor, and A. E. Underhill, *J. Chem. Soc. A* 128 (1968).

<sup>324</sup> F. Holmes and F. Jones, *J. Chem. Soc.* 2398 (1960).

<sup>325</sup> R. Driver and W. R. Walker, *Australian J. Chem.* **21**, 671 (1968).

<sup>326</sup> N. C. Li, J. M. White, and E. Doody, *J. Am. Chem. Soc.* **76**, 6219 (1954).

<sup>327</sup> P. Brooks and N. Davidson, *J. Am. Chem. Soc.* **82**, 2118 (1960).

<sup>328</sup> N. C. Li, T. L. Chu, C. T. Fujii, and J. M. White, *J. Am. Chem. Soc.* **77**, 859 (1955).

<sup>329</sup> R. A. Plane and T. V. Long, *Acta Chem. Scand.* **17**, Suppl. 1, 391 (1963); *Chem. Abstr.* **60**, 811 (1964).

<sup>330</sup> C. Sandmark and C. I. Branden, *Acta Chem. Scand.* **21**, 993 (1967); *Chem. Abstr.* **67**, 58065 (1967).

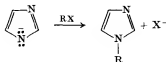
<sup>331</sup> J. T. Edsall, G. Felsenfeld, D. S. Goodman, and F. R. N. Gurd, *J. Am. Chem. Soc.* **76**, 3054 (1954).

<sup>332</sup> F. Seel and V. Sperber, *Angew. Chem. Intern. Ed. Engl.* **7**, 70 (1968).

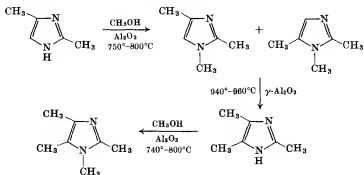
<sup>333</sup> J. G. Beestlestone, A. A. Epega, and D. H. Irvine, *J. Chem. Soc. A* 1346 (1968).

<sup>334</sup> A. V. Leshchenko, V. T. Panyushkin, A. D. Garnovskii, and O. A. Osipov, *Zh. Obshch. Khim.* **37**, 1069 (1967); *Chem. Abstr.* **67**, 104715 (1967).

an imidazole with an alkyl halide (or related compound) is commonly carried out in the presence of the oxide or hydroxide of an alkali metal or alkaline earth element,<sup>335</sup> sodium alkoxide,<sup>248</sup> or sodamide,<sup>210, 336</sup> with solvents such as ethanol,<sup>248</sup> dioxane,<sup>337</sup> acetone,<sup>338</sup> or liquid ammonia.<sup>210</sup> Best results are obtained using sodamide in liquid ammonia.<sup>221</sup> A recent report<sup>339</sup> of the use of sodium in liquid ammonia



with methyl iodide indicates yields of 52–72% of 1-methylbenzimidazole derivatives. Fournari and his co-workers<sup>214</sup> prepared *N*-methyl- and *N*-benzylimidazoles by reaction of potassium imidazolate with the halogen compound, either in a sealed tube or by refluxing the reagents in xylene, benzene, or toluene. 1-Alkyl-2-nitroimidazoles have been synthesized in a similar fashion.<sup>340</sup> High yields of alkylimidazoles are obtained by treatment of imidazole at 180°C with dimethyl



<sup>335</sup> Shell Internationale Research Maatschappij N.V., Netherlands Patent 6,706,104 (1967); *Chem. Abstr.* **68**, 59583 (1968).

<sup>336</sup> W. Schindler, U.S. Patent, 3,073,841 (1963); *Chem. Abstr.* **58**, 12574 (1963).

<sup>337</sup> S. Herrling, H. Keller, and H. Mueckter, German Patent, 1,000,384 (1957); *Chem. Abstr.* **54**, 1550 (1960).

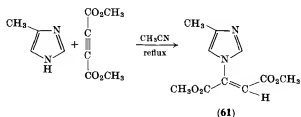
<sup>338</sup> A. F. Pozharskii and A. M. Simonov, *Zh. Obshch. Khim.* **33**, 179 (1963); *Chem. Abstr.* **69**, 600 (1963).

<sup>339</sup> R. M. Acheson, M. W. Foxton, P. J. Abbot, and K. R. Mills, *J. Chem. Soc. C* 885 (1967).

<sup>340</sup> A. G. Beaman, R. Duschinsky, and W. P. Tautz, U.S. Patent 3,391,156 (1968); *Chem. Abstr.* **69**, 96718 (1968).

oxalate<sup>341</sup> and by vapor-phase methylation with methanol in the presence of  $\text{Al}_2\text{O}_3$ .<sup>342</sup> The latter reaction is accompanied by catalytic rearrangement of an *N*-methyl group to C-4 or C-5, followed by remethylation at the 1-position. This vapor-phase reaction seems more likely to follow a free radical mechanism rather than to involve an electrophilic substitution pathway.

1-Allylimidazoles can be prepared by reaction of the imidazole with 3-chloro-1-propene in the presence of sodium hydroxide in acetonitrile.<sup>343</sup> Similarly, imidazoles can be alkylated in the 1-position by a variety of unsaturated compounds such as acetylene,<sup>344, 345</sup> acrylic acid derivatives,<sup>346, 347</sup> diazomethane,<sup>348</sup> and methyl acetylenedicarboxylate.<sup>339</sup> In the last-named reaction the adduct is probably the 4-isomer (61) rather than the 5-isomer due to the steric effect of the methyl group on conjugation of the 1-substituent with the ring. With



4,5-dicyanoimidazole, ethylene oxide in sodium hydroxide reacts to form 1-vinyl-4,5-dicyanoimidazole.<sup>156</sup> It is likely that most of these reactions with unsaturated compounds proceed via the imidazole anion.

Groups such as triphenylmethyl and glycosyl are difficult to

<sup>341</sup> H. Spaerig and A. Steimmig, Belgian Patent 656,675 (1965); *Chem. Abstr.* **64**, 19629 (1966).

<sup>342</sup> W. E. Erner, U.S. Patent 3,177,223 (1965); *Chem. Abstr.* **63**, 1795 (1965).

<sup>343</sup> N. Sawa and M. Kurita, Japanese Patent 4153 (1967); *Chem. Abstr.* **67**, 54128 (1967).

<sup>344</sup> M. Taniyama and N. Sawa, Japanese Patent 16027 (1961); *Chem. Abstr.* **56**, 12907 (1962).

<sup>345</sup> N. Sawa and S. Okamura, U.S. Patent 3,337,577 (1968); *Chem. Abstr.* **68**, 59582 (1968).

<sup>346</sup> A. M. Efros, *Zh. Obshch. Khim.* **30**, 3565 (1960); *Chem. Abstr.* **55**, 18712 (1961).

<sup>347</sup> W. B. Wheatley and G. F. Stiner, *J. Org. Chem.* **22**, 923 (1957).

<sup>348</sup> N. P. Bednyagina, I. N. Getsova, and I. Ya. Postovskii, *Zh. Obshch. Khim.* **32**, 3011 (1962); *Chem. Abstr.* **58**, 9050 (1963).



introduce directly into the 1-position, but this can be accomplished through the silver salts of imidazoles.<sup>349</sup>

Reductive removal of such groups as benzyl from the 1-position is readily achieved by reaction with sodium in liquid ammonia.<sup>54</sup>

d. *Arylation*. Imidazoles may be arylated directly using aryl halides in nitrobenzene in the presence of potassium carbonate and cuprous bromide catalyst.<sup>350-352</sup> The use of benzyne also leads to direct *N*-arylation of imidazoles.<sup>353</sup> 1-Fluoro-2,4-dinitrobenzene reacts with imidazoles in benzene (containing some triethylamine) to give 77-92% yields of the *N*-dinitrophenyl derivatives.<sup>354</sup>

e. *Acylation*. Imidazoles carrying acyl substituents on nitrogen are implicated in certain biological processes, such as the catalytic activity of some hydrolytic enzymes.<sup>320, 355</sup> Among the methods of synthesis of such compounds are reaction with potassium cyanate in neutral medium (to give the *N*-carbamoylimidazole),<sup>356</sup> treatment of imidazole with ketene in benzene solution,<sup>357</sup> reaction with isopropenyl acetate,<sup>358</sup> reaction with acetyladenosine monophosphate,<sup>359</sup> reaction with chlorides of aromatic sulfonic acids in the presence of weak bases,<sup>360</sup> and treatment of *N*-(trimethylsilyl)imidazole with acid chlorides.<sup>361</sup> The two most commonly used methods are, however, reaction of a 1:2 molar mixture of acid chloride and imidazole in an inert solvent at room temperature, and reaction of free carboxylic

<sup>349</sup> H. Giesemann, H. Lettau, and H.-G. Mannsfeldt, *Chem. Ber.* **93**, 570 (1960).

<sup>350</sup> A. F. Pozharskii, B. K. Martsokha, and A. M. Simonov, *Zh. Obshch. Khim.* **33**, 1005 (1963); *Chem. Abstr.* **59**, 7515 (1963).

<sup>351</sup> B. K. Martsokha, A. F. Pozharskii, and A. M. Simonov, *Zh. Obshch. Khim.* **34**, 1317 (1964); *Chem. Abstr.* **61**, 1849 (1964).

<sup>352</sup> L. M. Sitkina and A. M. Simonov, *Khim. Geterotsikl. Soedin., Akad. Nauk. Latv. SSR* **143** (1966); *Chem. Abstr.* **65**, 13686 (1966).

<sup>353</sup> A. F. Pozharskii, T. M. Meleshko and A. M. Simonov, *Khim. Geterotsikl. Soedin., Akad. Nauk. Latv. SSR* **473** (1966); *Chem. Abstr.* **65**, 8895 (1966).

<sup>354</sup> J. K. F. Wilshire, *Australian J. Chem.* **19**, 1935 (1966).

<sup>355</sup> E. A. Barnard and W. D. Stein, *Advan. Enzymol.* **20**, 51 (1958).

<sup>356</sup> J. M. Lowenstein, *J. Chem. Soc.* 4667 (1956).

<sup>357</sup> R. D. Kimbrough, *J. Org. Chem.* **29**, 1242 (1964).

<sup>358</sup> J. H. Boyer, *J. Am. Chem. Soc.* **74**, 6274 (1952).

<sup>359</sup> W. P. Jencks, *Biochim. Biophys. Acta* **24**, 227 (1957); *Chem. Abstr.* **51**, 12176 (1957).

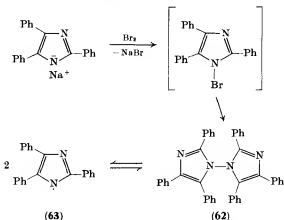
<sup>360</sup> S. S. Tiwari and A. Swaroop, *J. Indian Chem. Soc.* **39**, 195 (1962); *Chem. Abstr.* **57**, 5902 (1962).

<sup>361</sup> L. Birkofer, P. Richter, and A. Ritter, *Ber.* **93**, 2804 (1960).

acids with *N,N'*-carbonyldiimidazole at room temperature.<sup>362</sup> 1-Acetyl derivatives of 2-mercaptoimidazoles (or 2-hydroxyimidazoles) are obtained by heating with acetic anhydride in pyridine (*S*-acylation occurs when the reaction medium is absolute ethanol).<sup>363</sup>

Reddy *et al.*<sup>220</sup> prepared the 1-acetyl derivatives of a number of imidazoles by dissolving the compounds in acetic anhydride and evaporating the mixture *in vacuo*. With 2-methylimidazole they obtained a product which was analyzed on an equimolecular combination of the expected 1-acetyl-2-methylimidazole and acetic acid. They explained this result by the formation of a salt or complex with acetic acid.

f. *Halogenation*. Although imidazoles react with halogens to yield *C*-halogen derivatives, it has been discovered<sup>364</sup> that *N*-halo compounds are intermediates in the reaction. Thus, reaction of 2,4,5-triarylimidazoles (sodium salts) with bromine in dry ether yields *N,N'*-diimidazolyls (**62**). As all the ring carbon atoms are substituted,



no rearrangement to *C*-haloimidazoles can occur. Compounds such as (**62**) readily form radicals (**63**) by homolytic cleavage of the *N*-*N* bond,<sup>364, 365</sup> and these free radicals have been claimed<sup>365</sup> to be the

<sup>362</sup> H. A. Staab, M. Lüking, and F. H. Dürr, *Ber.* **95**, 1275 (1962).

<sup>363</sup> I. B. Simon and I. I. Kovunovskaya-Levshina, *Khim. Geterotsikl. Soedin., Akad. Nauk. Latv. SSR* 758 (1966); *Chem. Abstr.* **67**, 3037 (1967).

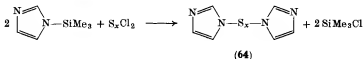
<sup>364</sup> H. Baumgaertel and H. Zimmermann, *Z. Naturforsch.* **18b**, 406 (1963); *Chem. Abstr.* **59**, 6382 (1963).

<sup>365</sup> T. Hayashi and K. Maeda, *Bull. Chem. Soc. Japan* **35**, 2057 (1962).

essential intermediates in the process of chemiluminescence of *N,N'*-diimidazolyls.

g. *Hydroxyalkylation*. The hydroxyalkyl group may be introduced at position 1 of the imidazole ring either by the use of ethylene oxide in formic acid,<sup>366</sup> or with ethylene carbonate as solvent and reagent at 100°–145°C.<sup>367–369</sup>

h. *Miscellaneous*. When cyanogen bromide reacts with an imidazole with a free NH group a 1-cyanoimidazole is formed.<sup>370</sup> *N*-phosphoryl-,<sup>371, 372</sup> *N*-trimethylsilyl-,<sup>361</sup> *N*-sulfonyl-,<sup>373</sup> and *N*-borylimidazoles<sup>374</sup> are also prepared by electrophilic attack at the multiply bonded nitrogen. The *N*-trimethylsilylimidazoles readily react with acyl chlorides to yield *N*-acyl derivatives<sup>361</sup> and with chlorosulfanes to yield diimidazolylsulfanes (64).<sup>375</sup> The synthesis of 1-(ethoxy-



carbonylmethyl)-2-methylimidazole has been accomplished by reaction of ethyl chloroacetate with the conjugate base of 2-methylimidazole.<sup>376</sup>

## 2. At Ring Carbon Atoms

The effect of two nitrogen atoms in the five-membered imidazole ring should result in more ready halogenation and approximately

<sup>366</sup> C. Podesva and K. Vagi, French Patent 1,379,915 (1965); *Chem. Abstr.* **62**, 9145 (1965).

<sup>367</sup> R. Sannicolo, U.S. Patent 3,178,446 (1965); *Chem. Abstr.* **63**, 610 (1965).

<sup>368</sup> N. Sawa, Japanese Patent 13,872 (1965); *Chem. Abstr.* **63**, 13274 (1965).

<sup>369</sup> Instituto Luso-Farmaco S a r.l., British Patent 939,681 (1963); *Chem. Abstr.* **60**, 2949 (1964).

<sup>370</sup> H. Giesemann, *J. Prakt. Chim.* **1**, 345 (1955); *Chem. Abstr.* **54**, 2313 (1960).

<sup>371</sup> J. Baddiley, J. G. Buchanan, and R. Letters, *J. Chem. Soc.* 2812 (1956).

<sup>372</sup> L. N. Nikolenko and E. V. Degterev, *Zh. Obshch. Khim.* **37**, 1350 (1967); *Chem. Abstr.* **68**, 59490 (1968).

<sup>373</sup> H. A. Staab and K. Wendel, *Ann.* **694**, 78 (1966).

<sup>374</sup> S. Trofimenko, *J. Am. Chem. Soc.* **89**, 3903 (1967).

<sup>375</sup> F. Fehér and B. Degen, *Angew. Chem. Intern. Ed. Engl.* **6**, 703 (1967).

<sup>376</sup> J. Toth, L. Boor, A. Gorgenyi, D. Bor, and S. Gorog, Hungarian Patent 154,810 (1968); *Chem. Abstr.* **69**, 96719 (1968).

equivalent ease of nitration and sulfonation compared with benzene. Nitration and sulfonation occur initially in the 4- and 5-positions,<sup>317</sup> whereas diazo coupling prefers the 2-position.<sup>377</sup> A number of kinetic studies of iodination<sup>318, 377-380</sup> and diazo coupling,<sup>378</sup> along with improvements in quantum mechanical calculations on the molecule, have aided in the solution of the problem. It now seems apparent that halogenation and diazo coupling involve the conjugate base of imidazole<sup>381</sup> (iodination even involves the imidazole anion at pH 7). Iodination, however, occurs initially at the 4- or 5-positions<sup>379, 381</sup> (probably via the *N*-iodo compound<sup>384</sup>), whereas diazo coupling occurs at position 2 unless the imino nitrogen or position 2 is substituted.<sup>318</sup> Although both reactions involve the same intermediate (the conjugate base of imidazole), iodination follows the values of the localization energies and depends on the transition state of the reaction with proton removal as the rate-determining step, whereas diazo coupling follows the pathway predicted by charge densities.<sup>382</sup>

Electrophilic substitution of nitro and sulfonic acid groups occurs in strongly acid media and involves attack on the conjugate acid of imidazole—a system exhibiting pronounced deactivation. Electron density calculations<sup>294, 296, 297</sup> predict the experimentally found substitution at positions 4 and 5. Acylation under Friedel-Crafts conditions does not occur in imidazoles.

Substituent effects follow the general pattern of substituted benzene derivatives in that nitro, sulfonic acid, and carboxyalkyl groups deactivate the ring to further substitution, whereas amino and methoxy groups strongly activate, and methyl and chloro groups have little effect. Ridd<sup>383</sup> has recently reviewed electrophilic substitutions on quinoline, pyridine, and imidazole.

a. *Halogenation.* Imidazoles are readily halogenated (e.g., Br<sub>2</sub>-CHCl<sub>3</sub> gives 2,4,5-tribromoimidazole<sup>384</sup>) in the absence of catalysts

<sup>377</sup> R. D. Brown, H. C. Duffin, J. C. Maynard, and J. H. Ridd, *J. Chem. Soc.* 3937 (1953).

<sup>378</sup> J. H. Ridd, *J. Chem. Soc.* 1238 (1955).

<sup>379</sup> A. Grimison and J. H. Ridd, *J. Chem. Soc.* 3019 (1959).

<sup>380</sup> J. D. Vaughan, D. G. Lambert, and V. L. Vaughan, *J. Am. Chem. Soc.* **86**, 2857 (1964).

<sup>381</sup> L. Schutte, P. P. Kluit, and E. Havinga, *Tetrahedron Suppl.* **7**, 295 (1966).

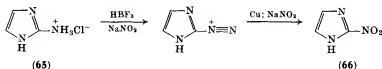
<sup>382</sup> J. M. Bassett and R. D. Brown, *J. Chem. Soc.* 2701 (1954).

<sup>383</sup> J. H. Ridd, *Z. Chem.* **8**, 201 (1968).

<sup>384</sup> I. E. Balaban and F. L. Pyman, *J. Chem. Soc.* 947 (1922).

required for the halogenation of benzene. Even in the presence of the strongly deactivating nitro group halogenation can still occur. The use of hypochlorite solutions to prepare 4,5-dichloro- and 2,4,5-trichloroimidazoles,<sup>385</sup> and the chlorination of imidazole and *C*-alkyl imidazoles with *N*-chlorophthalimide<sup>386</sup> have been reported. Bromoimidazoles can be converted into chloroimidazoles by refluxing in hydrochloric acid.<sup>385</sup> Ring opening occurs when imidazole reacts with bromine at low acidities.<sup>317</sup>

b. *Nitration and Sulfonation.* Both nitration and sulfonation of imidazoles take place at the 4- or 5-positions, involve the conjugate acid, and require somewhat more vigorous conditions than for the benzene ring.<sup>317, 387</sup> Thus, although 4-nitroimidazoles are readily prepared,<sup>259, 388-392</sup> 2-nitroimidazoles (66) must be approached through the corresponding 2-amino compound (65).<sup>393-396</sup> When



<sup>385</sup> A. W. Lutz and S. DeLorenzo, *J. Heterocycl. Chem.* **4**, 399 (1967).

<sup>386</sup> J. L. Imbach, R. Jacquier, and A. Romani, *J. Heterocycl. Chem.* **4**, 451 (1967).

<sup>387</sup> M. W. Austin, M. Brickman, J. H. Ridd, and B. V. Smith, *Chem. Ind.* (London) 1057 (1962).

<sup>388</sup> K. Butler, H. L. Howes, J. E. Lynch, and D. K. Pirie, *J. Med. Chem.* **10**, 891 (1967).

<sup>389</sup> M. Hoffer, U.S. Patent 3,341,548 (1967); *Chem. Abstr.* **68**, 105198 (1968).

<sup>390</sup> P. M. Kochergin, *Khim. Geterotsikl. Soedin., Akad. Nauk. Latv. SSR* 761 (1965); *Chem. Abstr.* **64**, 9709 (1966).

<sup>391</sup> C. Cosar, C. Crisan, R. Horelois, R. R. M. Jacob, J. Robert, S. Tchelitcheff, and R. Vaupre, *Arzneimittel-Forsch.* **16**, 23 (1966); *Chem. Abstr.* **66**, 2512 (1967).

<sup>392</sup> G. P. Ellis, C. Epstein, C. Fitzmaurice, L. Goldberg, and G. H. Lord, *J. Pharm. Pharmacol.* **16**, 801 (1964).

<sup>393</sup> G. C. Lancini and E. Lazzari, *Experientia* **21**, 83 (1965); *Chem. Abstr.* **62**, 9121 (1965).

<sup>394</sup> A. G. Beaman, W. Tautz, T. Gabriel, and R. Duschinsky, *J. Am. Chem. Soc.* **87**, 389 (1965).

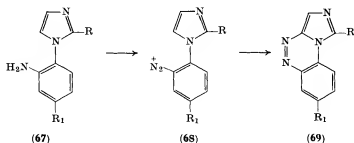
<sup>395</sup> Lepetit S. p. A., Netherlands Patent 6,510,485 (1966); *Chem. Abstr.* **65**, 724 (1966).

<sup>396</sup> A. G. Beaman, R. Duschinsky, and W. P. Tautz, U.S. Patent 3,255,201 (1966); *Chem. Abstr.* **65**, 13724 (1966).

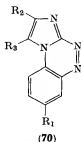
imidazole nitrate is heated with sulfuric acid, or when sodium nitrate is added to imidazole, the 4-nitro compound is formed.<sup>391, 392</sup>

c. *Nitrosation*. Under alkaline conditions (e.g., sodium ethoxide) alkyl nitrites nitrosate imidazoles possessing an unsubstituted imino nitrogen in the 4-position.<sup>397</sup>

d. *Diazo Coupling*. When positions 1 and 2 of the imidazole ring are unsubstituted, diazo coupling occurs preferentially at C-2, although when this position is blocked coupling can take place at C-4 or C-5. Simonov *et al.*<sup>398</sup> have recently reported an unusual coupling reaction in the imidazole series. Salts of the *o*-(imidazol-1-yl)phenyldiazonium ion (68), formed by diazotization of *N*-(*o*-aminophenyl)imidazoles (67) at pH 5-6 undergo an intermolecular azo coupling at position 5 to form an imidazo[5,1-*c*][1,2,4]benzotriazine (69).



If the 5-position is blocked, coupling can occur at C-2, but with greater difficulty, to yield a disubstituted derivative (70) of imidazo[1,2-*c*][1,2,4]benzotriazine. As the reaction does not occur below pH 4,



<sup>397</sup> S. Cusmano and M. Ruccia, *Gazz. Chim. Ital.* **88**, 463 (1958).

<sup>398</sup> A. M. Simonov, L. M. Sitkina, and A. F. Pozharskii, *Chem. Ind.* (London) 1454 (1967).

then it is likely that the unprotonated imidazole ring participates, and the driving force for the reaction could be the tendency for ring closure to produce the imidazobenzotriazine system.

e. *Miscellaneous.* Imidazole-4,5-dicarboxylic acids are prepared by the reaction of carbon dioxide with imidazole (or 2-alkylimidazoles) at 260°C/50 atm. in the presence of potassium carbonate and cadmium fluoride.<sup>399</sup>

Imidazoles substituted in the 1-position can be hydroxymethylated at C-2 with formaldehyde or paraformaldehyde,<sup>400, 401</sup> whereas imidazoles unsubstituted at N-1 are hydroxymethylated at C-4 or C-5. For example, 4-methylimidazole yields 4-methyl-5-hydroxymethylimidazole.<sup>402</sup> If there is a deactivating substituent in the ring (e.g., 4-nitroimidazole) hydroxymethylation will not take place. Thermal condensation of *N*-substituted imidazoles with other aldehydes (except acetaldehyde) or the reaction of aldehydes with 2-lithioimidazoles results in the formation of 2-hydroxyalkylimidazoles.<sup>210</sup>

#### D. NUCLEOPHILIC ATTACK

##### 1. At Ring Carbon Atoms

Among the reactions of this type are substitutions of imidazole diazonium salts,<sup>393, 394</sup> halogenoimidazoles,<sup>385, 403-405</sup> imidazolones,<sup>386</sup> and a number of other reactions including metallation.

Halogen atoms, particularly in the 2-position, are replaceable by aminoalkyl, alkoxyl, hydroxy, or thiol groups. It is a general rule that groups in the 2-position of the imidazole ring are more readily displaced by nucleophiles than those in the 4- and 5-positions. Nucleophilic displacement of halogen is easier if an electron-withdrawing substituent is present. For example, 4-nitro-5-bromoimidazole reacts with sulfite ion to produce the corresponding 4-nitro-5-sulfonic acid.<sup>404</sup>

<sup>399</sup> Henkel and Cie. G.m.b.H., British Patent 816,531 (1959); *Chem. Abstr.* **54**, 1552 (1960).

<sup>400</sup> P. C. Jocelyn, *J. Chem. Soc.* 3305 (1957).

<sup>401</sup> J. Kollonitsch, U.S. Patent 3,290,328 (1966); *Chem. Abstr.* **66**, 55488 (1967).

<sup>402</sup> A. J. Ewins, *J. Chem. Soc.* 2052 (1911).

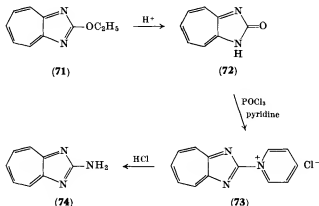
<sup>403</sup> A. Ricci and P. Vivarelli, *J. Chem. Soc. B* 1280 (1968).

<sup>404</sup> I. E. Balaban and F. L. Pyman, *J. Chem. Soc.* 1564 (1924).

<sup>405</sup> I. E. Balaban, *J. Chem. Soc.* 2423 (1932).

This substitution does not occur with cyanide as the nucleophile, nor with a carboxyl group in the place of the nitro group.<sup>405</sup> Nucleophilic displacement of halogen by thiophenol occurs in 1-substituted 2-halogenobenzimidazoles.<sup>403</sup>

Whereas the ethoxyl group of 2-ethoxycycloheptimidazole (71) is readily replaced by dialkylamino and by halogen,<sup>97</sup> when the corresponding cycloheptimidazol-2(1*H*)-one (72) is treated with phosphoryl chloride in pyridine, very little of the 2-chloro compound is formed. The major product is a pyridinium derivative (73) which breaks down with hydrochloric acid to 2-aminocycloheptimidazole (74).<sup>97</sup>



Only condensed imidazoles will enter into the Chichibabin reaction.<sup>406</sup> Sulfo groups on C-2 of benzimidazoles are replaced by chloro,<sup>407</sup> cyano,<sup>408</sup> hydroxy,<sup>409, 410</sup> and alkylamino groups,<sup>411</sup> and the

<sup>406</sup> A. M. Simonov and A. D. Garnovskii, *Zh. Obshch. Khim.* **31**, 114 (1961); *Chem. Abstr.* **55**, 22298 (1961).

<sup>407</sup> H. Balli and F. Kersting, *Ann. Chem.* **647**, 1 (1961); *Chem. Abstr.* **56**, 10133 (1962).

<sup>408</sup> W. Zerweck, H. Salkowski, and W. Kunze, German Patent 613,067 (1935); *Chem. Abstr.* **29**, 5461 (1935).

<sup>409</sup> I. G. Farbenind. A.-G., French Patent 779,282 (1935); *Chem. Abstr.* **29**, 4774 (1935).

<sup>410</sup> E. Herdieckerhoff and E. Tschunkur, German Patent 615,131 (1935); *Chem. Abstr.* **29**, 6250 (1935).

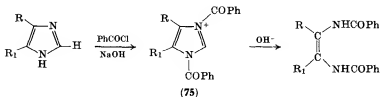
<sup>411</sup> E. Herdieckerhoff, W. Zerweck, and H. Salkowski, German Patent 617,544 (1935); *Chem. Abstr.* **30**, 734 (1936).



methylthio substituent can be replaced by amino<sup>412</sup> and hydrazine<sup>413</sup> groups. Reaction of phosphorus oxychloride with imidazol-2-one leads to the formation of 2-chloroimidazole.<sup>386</sup>

Metallation of 1-alkyl- (or aralkyl-)imidazoles at low temperatures with butyllithium produces 2-lithioimidazoles,<sup>210</sup> although small quantities of the 5-lithioimidazoles may also be formed.<sup>414</sup>

In the cationic form, imidazoles are readily attacked by hydroxide ion. The cleavage of the imidazole ring by the Bamberger degradation reaction<sup>415</sup> probably occurs by attack of hydroxide ion on compounds of structure (75). In view of the great stability of the imidazole ring this is a remarkable reaction.



The formation of "pseudo-bases" when hydroxide ions attack 1,3-dialkylimidazolium salts<sup>416</sup> is a further example of this type of reaction.

Some recent experiments by Harris and Randall<sup>226a</sup> on hydrogen-deuterium exchange of 1-methylimidazole-2,4,5-*d*<sub>3</sub> (carried out in NMR tubes at 26°C with solutions of varying pH) indicate that exchange at the 2-position is effected by nucleophilic attack of hydroxide ion on the conjugate acid of 1-methylimidazole. The exchange rate was found to be relatively unaffected on the alkaline side, but rapidly dropped to zero on the acid side.

## 2. At the NH Group

Nucleophilic reactions of this type are a result of the weakly acidic nature of the "pyrrole-type" nitrogen in the imidazole ring. These acidic properties are slightly more pronounced than those of pyrrole

<sup>412</sup> D. J. Brown, *J. Chem. Soc.* 1974 (1958).

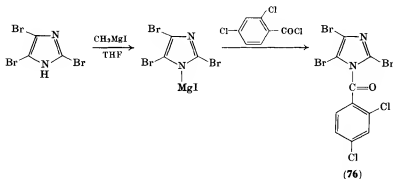
<sup>413</sup> N. P. Bednyagina, I. N. Getsova, and I. Ya. Postovskii, *Zh. Obshch. Khim.* **32**, 3015 (1962); *Chem. Abstr.* **58**, 9050 (1963).

<sup>414</sup> D. A. Shirley and P. W. Alley, *J. Am. Chem. Soc.* **79**, 4922 (1957).

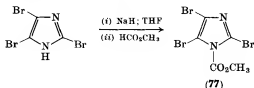
<sup>415</sup> E. Bamberger, *Ann.* **273**, 267 (1893).

<sup>416</sup> A. M. Simonov, N. D. Vitkevich, and S. Ya. Zheltonozhko, *Zh. Obshch. Khim.* **30**, 2681 (1960); *Chem. Abstr.* **55**, 15467 (1961).

owing to the inductive effect of the tertiary nitrogen. Salts are formed with a number of metals; e.g., a sparingly soluble silver salt is formed with ammoniacal silver nitrate,<sup>349</sup> and alkali metal salts are produced by reaction with the metal in liquid ammonia. The presence of electron-withdrawing substituents increases the acidity.<sup>176</sup> *N*-Imidazolyl Grignard reagents are formed by reaction with an alkyl magnesium halide, and have been used, e.g., in the synthesis of 1-(2',4'-dichlorobenzoyl)-2,4,5-tribromoimidazole (76).<sup>417</sup> A similar



reaction of the same mechanistic class leads to methyl 2,4,5-tribromoimidazole-1-carboxylate (77).<sup>417</sup>



### E. REACTIONS INVOLVING RADICALS

There have been very few references to free radical reactions in imidazole chemistry.

Calculations of free valences and localization energies<sup>418</sup> point to preferential radical attack at the 2-position in the neutral molecule,

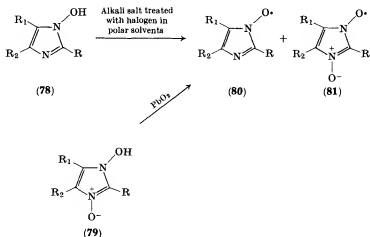
<sup>417</sup> Boots Pure Drug Co. Ltd., Netherlands Patent, 6,609,596 (1967); *Chem. Abstr.* 67, 64398 (1967).

<sup>418</sup> R. D. Brown, *Australian J. Chem.* 8, 100 (1955).

and in the 4-position in the anion. There is no clear-cut experimental evidence of the reactivity of imidazole toward radicals, although the reported bromination by cyanogen bromide in ether,<sup>309</sup> in which the 2-position is preferred, might occur by attack on the uncharged molecule by bromine atoms. Furthermore, the rearrangements of 1-alkylimidazoles at high temperatures<sup>227, 240, 342, 419-421</sup> might follow a free radical course. Sealed-tube reactions of 1-methylimidazole under nitrogen result in the formation of 2-methylimidazole and imidazole, along with smaller quantities of 4-methylimidazole and di- and trisubstituted products.<sup>240</sup> A similar series of isomerizations is apparent with 1-ethylimidazole.<sup>240</sup> Photoisomerization of 1,4,5-trimethylimidazole results in the formation of a 5:1 mixture of 1,2,5-trimethylimidazole and the starting material, whereas the corresponding 1-methyl-4,5-diphenyl compound did not react under the same conditions (42 hours under a low-pressure mercury lamp).<sup>227</sup>

It is possible that free radicals participate in the formation of 2-mercaptoimidazoles when imidazoles are heated with sulfur.<sup>310</sup>

Dehydrogenation of imidazol-1-ol (**78**) and its *N*-oxide (**79**) produces *N*-oxides (**80**) and *N,N'*-dioxides (**81**) of imidazoys.<sup>422</sup>



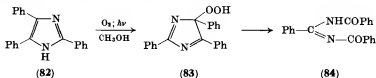
<sup>419</sup> O. Wallach, *Ber.* **16**, 534 (1883).

<sup>420</sup> A. Windaus, *Ber.* **39**, 3886 (1906).

<sup>421</sup> H. A. D. Jowett and S. Potter, *J. Chem. Soc. Trans.* **83**, 464 (1903).

<sup>422</sup> K. Volkamer, H. Baumgärtel, and H. Zimmermann, *Angew. Chem. Intern. Ed. Engl.* **6**, 947 (1967).

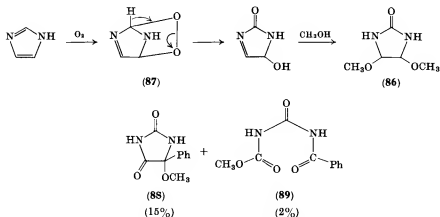
In a study of the photosensitized oxygenation of imidazoles, Wasserman *et al.*<sup>423</sup> found that 2,4,5-triphenylimidazole (**82**) reacts with singlet oxygen to yield an *N,N'*-diaroylbenzamidine (**84**),



probably through the hydroperoxide (**83**). Similarly, 1,2,4,5-tetraphenylimidazole gives *N,N'*-dibenzoyl-*N*-phenylbenzamidine (**85**) in 97% yield.



Imidazole reacts very slowly with singlet oxygen to form the imidazolidone (**86**)<sup>423</sup> through an elimination reaction involving proton loss and cleavage of the oxygen-oxygen bond of the transannular peroxide (**87**). On the other hand, 4-phenylimidazole forms a hydantoin derivative (**88**) and *N*-benzoyl-*N'*-methoxycarbonylurea (**89**). This



<sup>423</sup> H. H. Wasserman, K. Stiller, and M. B. Floyd, *Tetrahedron Letters* 3277 (1968).

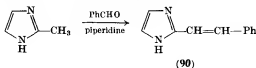
latter case is clearly in line with the uptake of more than one mole of oxygen per mole of substrate and is therefore parallel with oxygenation of histidine in the photooxidative inactivation of some enzymes.

The photolysis of 4-imidazolin-2-one has been studied.<sup>424</sup>

## F. REACTIONS OF SUBSTITUENTS ON RING CARBON ATOMS

### 1. Alkyl and Aryl Groups

Methyl substituents in the 2-position are active because of electron deficiency, but those in the 4- and 5-positions act as if they were attached to a benzene ring. Hence, 2-methylimidazole condenses with benzaldehyde to form 2-styrylimidazole (**90**).<sup>425</sup>



Alkyl and fused aryl substituents (as in benzimidazoles) are oxidized by permanganate to carboxyl substituents. Oxidation of methylimidazoles with selenium dioxide is only useful in the case of benzimidazoles for the synthesis of imidazole aldehydes.<sup>426</sup> The chemiluminescence of aryl-substituted imidazoles has been studied.<sup>427</sup>

### 2. Hydroxyalkyl Groups

Hydroxyalkyl groups can be converted into haloalkyl<sup>255</sup> (using thionyl chloride), reduced to the alkyl,<sup>54</sup> and oxidized to carboxylic acids<sup>428</sup> or aldehydes or ketones.<sup>189, 210, 429-431</sup> Although it is possible

<sup>424</sup> S. Guido, *Ber.* **101**, 3688 (1968).

<sup>425</sup> W. E. Erner and H. A. Green, U.S. Patent 3,050,520 (1960); *Chem. Abstr.* **57**, 15120 (1963).

<sup>426</sup> H. Schubert and G. Böhme, *Wiss. Z. Martin Luther Univ.* **8**, 1037 (1959); *Chem. Abstr.* **55**, 12389 (1961).

<sup>427</sup> E. H. White and M. J. C. Harding, *Photochem. Photobiol.* **4**, 1129 (1965); *Chem. Abstr.* **64**, 14065 (1966).

<sup>428</sup> R. A. Turner, C. F. Huebner, and C. R. Scholtz, *J. Am. Chem. Soc.* **71**, 2801 (1942).

<sup>429</sup> F. L. Pyman, *J. Chem. Soc.* 186 (1916).

<sup>430</sup> P. E. Iversen and H. Lund, *Acta Chem. Scand.* **20**, 2649 (1966); *Chem. Abstr.* **66**, 104953 (1967).

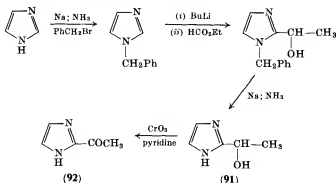
<sup>431</sup> A. M. Simonov and L. M. Sitkina, USSR Patent 178,384 (1966); *Chem. Abstr.* **64**, 19630 (1966).

to obtain imidazole-4-carboxaldehyde by oxidation of 4-hydroxymethylimidazole with nitric acid,<sup>429</sup> this is not possible with the 2-isomer, when selenium dioxide oxidation<sup>430, 431</sup> (often in dioxan<sup>431</sup>) of the 1-substituted 2-hydroxymethyl derivative is necessary. Imidazole-2-carboxaldehyde has also been prepared in 70% yield from 2-hydroxymethylimidazole using a sixfold excess of activated manganese dioxide in anhydrous ether, acetone, or carbon tetrachloride.<sup>186</sup> We have found<sup>432</sup> that good yields of imidazole-4-carboxaldehyde can be obtained using the same reagent. Polyhydroxyalkyl groups on imidazole are cleaved to aldehydes by periodate.<sup>55, 433</sup>

### 3. Aldehyde and Ketone Groups

The kinetics and mechanism of the reaction of imidazole-4-carboxaldehyde with hydroxylamine to form the oxime has been studied,<sup>188</sup> and some Schiff's bases of 2-formylbenzimidazole have been examined.<sup>434</sup>

As the imidazole nucleus does not undergo Friedel-Crafts acylation, ketone substituents must be introduced indirectly, either before the ring is formed<sup>34, 41, 210, 275, 435</sup> or by modification of existing substituents.<sup>210</sup> Roe<sup>210</sup> prepared 2-acetylimidazole (**92**) by oxidation of 1-(imidazol-2'-yl)ethanol (**91**) with chromic oxide in pyridine. The acyl-substituted imidazoles have distinctive infrared and ultraviolet



<sup>432</sup> K. H. Ong and M. R. Grimmett, unpublished observation.

<sup>433</sup> J. Fernandez-Bolanos and M. Mendenez Gallego, *Anales Real. Soc. Espan. Fis. Quim. (Madrid)*, Ser. B **62**, 1005 (1966); *Chem. Abstr.* **67**, 90719 (1967).

<sup>434</sup> S. Kolka, *Zeszyty Nauk., Mat., Fiz. Chem.* **7**, 155 (1967).

<sup>435</sup> E. Ochiai, Y. Tamamushi, and F. Nagasawa, *Ber.* **73**, 28 (1940).

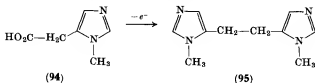
spectra, and the 2-acetyl compounds appear to be more volatile and more soluble in nonpolar solvents than other imidazoles with unsubstituted NH groups.<sup>435</sup> This phenomenon may be due to intramolecular hydrogen bonding between the imino and carbonyl functions (as in **93**) competing with the normal intermolecular N-H...N bonds which are formed in nonpolar solvents and in the liquid and crystalline states.



#### 4. Carboxyl Groups

Decarboxylation procedures, which have been discussed by Schipper and Day,<sup>2</sup> require fairly high temperatures.

Imidazole carboxylic acids are readily converted into hydrazides,<sup>436</sup> acid halides,<sup>437</sup> amides,<sup>437-439</sup> and esters,<sup>439, 440</sup> and they may be reduced to alcohols with lithium aluminum hydride,<sup>441</sup> and to aldehydes by controlled potential reduction.<sup>442</sup> Anodic oxidation of 1-methylimidazole-5-acetic acid (**94**) using cooled platinum electrodes yields 1,2-bis(1-methylimidazol-5-yl)ethane (**95**).<sup>443</sup>



<sup>436</sup> J. Nematollahi, W. Guess, and J. Autian, *J. Med. Chem.* **9**, 660 (1966).

<sup>437</sup> R. Weidenhagen and H. Wegner, *Ber.* **70**, 2309 (1937).

<sup>438</sup> I. E. Balaban, *J. Chem. Soc.* **2423** (1932).

<sup>439</sup> W. J. Palaveda and E. F. Schoenewaldt, U.S. Patent 2,905,692 (1959); *Chem. Abstr.* **54**, 14272 (1960).

<sup>440</sup> N. B. Vinogradova and N. V. Khromov-Borisov, *Metody Poluch. Khim. Reaktivov Prep.* No **14**, 40 (1966); *Chem. Abstr.* **67**, 3033 (1967).

<sup>441</sup> F. Farina, *Anales Real. Soc. Espan. Fis. Quim. (Madrid)*, **49**, 599 (1953); *Chem. Abstr.* **48**, 4524 (1954).

<sup>442</sup> P. E. Iversen and H. Lund, *Acta Chem. Scand.* **21**, 279 (1967).

<sup>443</sup> W. Doepke and G. D'Heureuse, *Z. Chem.* **8**, 184 (1968); *Chem. Abstr.* **69**, 27331 (1968).

### 5. Cyanide Substituents

Hydrolysis of 4,5-dicyanoimidazole yields 4-amino-5-imidazole-carboxamide which is converted by hypobromite into 4-amino-5-imidazole carbonitrile.<sup>444</sup> Hydrolysis of the dicyano compound with aqueous alkali yields the corresponding 4,5-dicarboxylic acid.<sup>156</sup> Reduction of the dicyanide with lithium aluminum hydride occurs with greater ease when the imino nitrogen carries a methyl substituent.<sup>156</sup>

### 6. Nitro Groups

Nitro groups, which are readily introduced into the imidazole ring,<sup>259, 388, 445</sup> can be reduced chemically or catalytically to amino groups.<sup>227, 446</sup> Nitro substituents facilitate the displacement of adjacent halogen substituents,<sup>447</sup> e.g., the chloro group of 5-chloro-4-nitroimidazole can be replaced by an alkylmercapto group using sodium alkylmercaptide and sodium ethoxide in ethanol.

### 7. Amino Groups

Aminoimidazoles do not appear to exist to any great extent in the tautomeric imino forms.<sup>448</sup> The *C*-amino groups have lower basic strength than aniline, and consequently alkylation occurs preferentially at a ring nitrogen. Amino substituents in the 2-position can generally be acylated and diazotized (usually in strongly acid medium), but 4-aminoimidazoles are more unstable and have not been extensively studied.

As 4-aminoimidazole-5-carboxamides have merited much interest as biosynthetic precursors of purines,<sup>449</sup> considerable effort has been

<sup>444</sup> Y. Yamada, I. Kumashiro, and T. Takenishi, *Bull. Chem. Soc. Japan* **41**, 241 (1968).

<sup>445</sup> M. Hoffer, U.S. Patent 3,341,548 (1967); *Chem. Abstr.* **68**, 105198 (1968).

<sup>446</sup> G. Hunter and J. A. Nelson, *Can. J. Res.* **19B**, 296 (1941); *Chem. Abstr.* **36**, 1321 (1942).

<sup>447</sup> H. Schubert, H. Simon, and A. Jurnar, *Z. Chem.* **8**, 62 (1968); *Chem. Abstr.* **68**, 95760 (1968).

<sup>448</sup> J. P. Ferris and L. E. Orgel, *J. Am. Chem. Soc.* **88**, 3829 (1966).

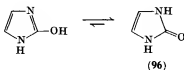
<sup>449</sup> J. Buchanan, in "Chemistry and Biology of the Purines," Boston, Massachusetts, 1957.



expended in the development of synthetic pathways leading to these and related products.<sup>450-455</sup>

### 8. Hydroxyl, Mercapto, and Related Groups

Existing experimental evidence, particularly from ultraviolet and infrared spectra,<sup>186, 456</sup> suggests that 2- and 4-hydroxyimidazoles exist predominantly in the azolone form (cf. 96). Since Pozharskii *et al.*<sup>3</sup> and Roger and Neilson<sup>457</sup> discussed methods of synthesis of



imidazolones up to 1964, further references have been made to their preparation<sup>458, 459</sup> and reactions.<sup>460</sup>

Mercaptoimidazoles resemble the hydroxy compounds in that they exist in the thione tautomeric forms. The thione group is readily removed with nitric acid,<sup>461</sup> ferric chloride,<sup>462</sup> oxygen in the presence of Pt-C catalyst,<sup>460</sup> nickel boride,<sup>463</sup> or, most commonly, Raney nickel.<sup>118, 460</sup>

When 1-methyl-2-*O*-alkyl (or 2-*S*-alkyl)imidazoles are heated, they undergo a Claisen rearrangement to the alkylimidazol-2-one (or

<sup>450</sup> E. Richter, J. E. Loeffler, and E. C. Taylor, *J. Am. Chem. Soc.* **82**, 3144 (1960).

<sup>451</sup> R. N. Naylor, G. Shaw, D. V. Wilson, and D. N. Butler, *J. Chem. Soc.* 4845 (1961).

<sup>452</sup> G. Shaw and D. V. Wilson, *J. Chem. Soc.* 2937 (1962).

<sup>453</sup> T. Shirodokoro, M. Fukuzawa, N. Ito, M. Yamada, and M. Kakehi, Japanese Patent 20,550 (1965); *Chem. Abstr.* **64**, 2096 (1966).

<sup>454</sup> Ajinomoto Co. Inc., French Patent 1,437,213 (1966); *Chem. Abstr.* **65**, 20136 (1966).

<sup>455</sup> N. P. Sen and P. L. McGeer, *J. Chromatog.* **20**, 147 (1965).

<sup>456</sup> R. Gompper and H. Herlinger, *Ber.* **89**, 2825 (1956).

<sup>457</sup> R. Roger and D. Neilson, *Chem. Rev.* **61**, 179 (1961).

<sup>458</sup> P. M. Kochergin, *Khim. Geterotsikl. Soedin* 749 (1966); *Chem. Abstr.* **66**, 104954 (1967).

<sup>459</sup> J. E. Scott, *Biochem. J.* **107**, 16 (1968).

<sup>460</sup> J. Fernandez-Bolanos, M. Lomas, D. Martinez Ruiz, and M. A. Pradera, *Anales Quim.* **64**, 203 (1968); *Chem. Abstr.* **69**, 52453 (1968).

<sup>461</sup> A. Wohl and W. Marckwald, *Ber.* **22**, 1353 (1889).

<sup>462</sup> A. O. Jackson and C. S. Marvel, *J. Biol. Chem.* **103**, 191 (1933).

<sup>463</sup> J. Clark, R. K. Grantham, and J. Lydiate, *J. Chem. Soc. C* 1122 (1968).

-2-thione).<sup>464</sup> The rearrangements of the corresponding *O*-allyl or *S*-allyl compounds proceed 15–20 times more rapidly.

### 9. Halogeno Groups

The syntheses and reactions of halogenoimidazoles have been discussed earlier in this review.

## G. REACTIONS OF SUBSTITUENTS ON RING NITROGEN ATOMS

Most of the reactions and properties of 1-substituted imidazoles have been discussed earlier in this review. Apart from the utilization of the readily removable benzyl substituent in synthetic procedures leading to 2-substituted imidazoles, perhaps the most exciting advances have stemmed from the reactions of the 1-acylimidazoles (imidazolides) which are extremely reactive in such nucleophilic reactions as hydrolysis and alcoholysis.<sup>12</sup> The use of such compounds as *N,N'*-carbonyldiimidazole in peptide synthesis is now commonplace. The silicon-nitrogen bond in *N*-trimethylsilylimidazoles is also extremely reactive, so reactive that it is attacked by  $\alpha$ -halogenocarboxylic esters.<sup>361</sup>

## H. MISCELLANEOUS

The imidazole aryne 1-methyl-4,5-dehydroimidazole undergoes ready addition reactions at the 4,5-bond.<sup>465</sup>

<sup>464</sup> K. M. Krivoozheiko and A. V. El'tsov, *Z. Org. Chem.* **4**, 1114 (1968); *Chem. Abstr.* **69**, 52070 (1968).

<sup>465</sup> T. Kauffmann, R. Nurnberg, J. Schulz, and R. Stabba, *Tetrahedron Letters* 4273 (1967).

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# The Chemistry of Lactim Ethers

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## I. Introduction

The chemistry of *O*-alkyl derivatives of lactams (lactim ethers) is one of the least studied aspects of lactam chemistry. The lactams themselves have been much investigated in the preparation of polymers, in connection with penicillin ( $\beta$ -lactams),<sup>1</sup> and also because of the tendency of certain substituted derivatives to ring-close to cyclols, cylopeptides, or cyclodepsipeptides.<sup>2,3</sup> A review on lactams has appeared.<sup>4</sup>

The application of lactams in heterocyclic synthesis depends on the activation of their amide function.<sup>5</sup> Similar activation of other functional groups, e.g., the conversion of ketones to enamines<sup>6</sup> and of carboxylic acid amides to imino ethers,<sup>7</sup> presented new applications for these compounds. Similarly, the conversion of lactams into lactim ethers offers a greater scope for the use of lactams in organic synthesis.

<sup>1</sup> I. L. Knunyants, B. L. Dyatkin, and N. P. Gambaryan, *Usp. Khim.* **25**, 785 (1956).

<sup>2</sup> V. K. Antonov, A. M. Shkrob, and M. M. Shemyakin, *Zh. Obshch. Khim.* **35**, 1380 (1965).

<sup>3</sup> V. K. Antonov, Doctoral Dissertation, Moscow, Institute of the Chemistry of Natural Compounds, 1966.

<sup>4</sup> Houben-Weyl, "Methoden der organischen Chemie," Vol. 11/2, p. 511. (1958).

<sup>5</sup> R. G. Glushkov, Candidate's Dissertation, Moscow, Institute of Organic Chemistry, 1961.

<sup>6</sup> J. Szmuszkowicz, *Advan. Org. Chem.* **4**, 1 (1963).

<sup>7</sup> R. Roger and D. G. Neilson, *Chem. Rev.* **61**, 179 (1961).

The chemical properties of lactim ethers have been briefly reviewed.<sup>8,9</sup> The present review surveys the reactions and use of lactim ethers in syntheses.

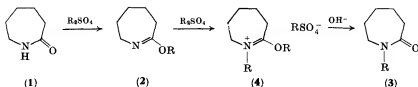
Lactim ethers are used in the synthesis of dyes<sup>10,11</sup> and other important classes of organic compounds. They are also of interest because of their biological activity<sup>12</sup> and use as accelerators for polymerization.<sup>13</sup>

## II. Methods of Synthesis of Lactim Ethers

### A. DIRECT ALKYLATION OF LACTAMS

The direct alkylation methods include the reaction of lactams with diazomethane<sup>14</sup> and the alkylation of metal salts of lactams with alkyl halides.<sup>15</sup> These two methods are not often used nowadays, because the alkylation can more conveniently be carried out with dialkyl sulfates or triethyloxonium fluoroborate.

A detailed study of the action of dialkyl sulfates on caprolactam (1) was undertaken by Benson and Cairns.<sup>16</sup> They found that the outcome depended on the molecular proportions of the reactants. Slow addition of the alkylating agent increased the yield of lactim ethers (2), whereas excess dialkyl sulfates decreased the yield because of the preferential formation of *N*-alkyl derivatives (3). Benson and Cairns proposed that 3 was formed via 2 and 4 as follows.



<sup>8</sup> S. Petersen, *Angew. Chem.* **64**, 602 (1952).

<sup>9</sup> S. Petersen and E. Tietze, *Med. Chem.* **7**, 262 (1963).

<sup>10</sup> H. Baumann and D. Leuchs, German Patent 1,098,646 (1961); *Chem. Abstr.* **55**, 27903 (1961).

<sup>11</sup> C. Schuster, R. Zeidler, R. Gehm, and D. Leuchs, German Patent 1,078,531 (1960); *Chem. Abstr.* **55**, 24041 (1961).

<sup>12</sup> W. A. Behrendt, *Arch. Intern. Pharmacodyn.* **147**, 99 (1964).

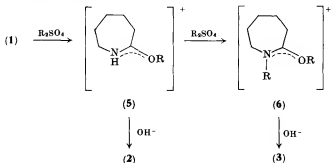
<sup>13</sup> R. B. Lund, P. W. Simon, E. W. Pietrusza, J. R. Pedersen, and H. K. Reimschuessel, Belgian Patent 638,901; *Chem. Abstr.* **62**, 10612 (1965).

<sup>14</sup> J. W. Ralls, *J. Org. Chem.* **26**, 66 (1961).

<sup>15</sup> W. C. Sumpter, *Chem. Rev.* **34**, 393 (1944).

<sup>16</sup> R. E. Benson and T. L. Cairns, *J. Am. Chem. Soc.* **70**, 2115 (1948).

According to Brederick *et al.*,<sup>17, 18</sup> the reaction of carboxylic acid amides with dialkyl sulfates proceeds via the intermediate ambident cation such as (5). In the case of caprolactam, when excess dialkyl sulfate is taken, the *N,O*-dialkyl derivative (6) is formed, which with base forms 3 (Scheme 1).



SCHEME I

In recent years the alkylation of lactams has been achieved using tertiary oxonium salts, particularly triethyloxonium fluoroborate.<sup>19, 20</sup> This reaction proceeds via cation formation (cf. 5). Treatment of the salt with base leads to the lactim ether.

The oxonium salts give better results than other alkylating agents.<sup>21</sup> Numerous examples of the application of oxonium salts for the alkylation of lactams<sup>21-27</sup> show that no *N*-alkyl derivatives could be isolated because of the high selectivity of oxonium salts in similar reactions.

<sup>17</sup> H. Brederick, F. Effenberger, and G. Simchen, *Ber.* **96**, 1350 (1963).

<sup>18</sup> H. Brederick, R. Gompper, H. Rempfer, K. Klemm, and H. Keck, *Ber.* **92**, 329 (1959).

<sup>19</sup> H. Meerwein, G. Hinz, P. Hofmann, E. Kroning, and E. Pfeil, *J. Prakt. Chem.* **147**, 257 (1937).

<sup>20</sup> H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Willfang, *J. Prakt. Chem.* **154**, 83 (1939).

<sup>21</sup> E. Profft and F. J. Becker, *J. Prakt. Chem.* **30**, 18 (1965).

<sup>22</sup> J. Harley-Mason and T. J. Leeney, *Proc. Chem. Soc. (London)*, 368 (1964).

<sup>23</sup> S. Petersen and E. Tietze, *Ann.* **623**, 166 (1959).

<sup>24</sup> R. G. Glushkov and O. Yu. Magidson, *Khim. Geterotsikl. Soedin.* No. 1, 85 (1965).

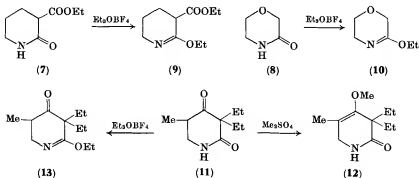
<sup>25</sup> R. G. Glushkov and O. Yu. Magidson, *Khim. Geterotsikl. Soedin.* No. 2, 240 (1965).

<sup>26</sup> M. Pesaro, J. Felner-Caboga, and A. Eschenmoser, *Chimia (Aarau)* **19**, 566 (1965).

<sup>27</sup> L. A. Paquette and T. J. Barton, *J. Am. Chem. Soc.* **89**, 5480 (1967).

The high tendency to *O*-alkylation by triethyloxonium fluoroborate compared with other alkylating agents is observed also in the alkylation of keto-enols,<sup>28</sup> the ambident ions of nitroparaffins,<sup>29, 30</sup> and potassium diethylthiophosphate.<sup>31</sup>

No comparison between trialkyloxonium fluoroborates and dialkyl sulfates has been made, but analysis of available data shows that oxonium salts are more generally applicable reagents for the preparation of lactim ethers. The alkylation of 3-carbethoxypiperid-2-one (7)<sup>25</sup> and morpholin-3-one (8)<sup>32</sup> with dimethyl sulfate failed, but with triethyloxonium fluoroborate these compounds gave 2-ethoxy-3-carbethoxy-3,4,5,6-tetrahydropyridine (9) and 3-ethoxy-3,4-dehydromorpholine (10) in excellent yield. The selective character of triethyloxonium fluoroborate is shown in its reaction with 3,3-diethyl-5-methylpiperidine-2,4-dione (11).<sup>25</sup> Reaction of 11 with the calculated quantity of dimethyl sulfate resulted in alkylation of the carbonyl group in position 4 with formation of 12, but reaction of 11 with triethyloxonium fluoroborate gave the lactim ether (13).



Recently, alkylation of lactams containing other functional groups such as cyano, carbethoxy, or secondary acylamino functions, with

<sup>28</sup> T. A. Mastryukova, A. E. Shipov, V. V. Abalyaeva, E. E. Kugucheva, and M. I. Kabachnik, *Dokl. Akad. Nauk SSSR* **164**, 340 (1964).

<sup>29</sup> L. G. Donaruma, *J. Org. Chem.* **22**, 1024 (1957).

<sup>30</sup> N. Kornblum and R. A. Brown, *J. Am. Chem. Soc.* **85**, 1359 (1963).

<sup>31</sup> T. A. Mastryukova, A. E. Shipov, V. V. Abalyaeva, E. M. Popov, and M. I. Kabachnik, *Dokl. Akad. Nauk SSSR* **158**, 1373 (1964).

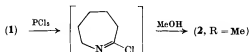
<sup>32</sup> R. G. Glushkov and O. Yu. Magidson, *Khim. Geterotsikl. Soedin.* No. 2, 192 (1966).

triethyloxonium fluoroborate has been reported.<sup>25, 33-41</sup> In all these cases the authors observed selective alkylation of lactams to lactim ethers. In some cases the starting material was isolated in the reaction of lactams with triethyloxonium fluoroborate, the reaction of the ambident cation with hydroxyl ion (during attempted isolation of the lactim ether) being given as an explanation.

Trialkyloxonium fluoroborates give better yields of lactim ethers than other alkylating agents because of the selectivity of these reagents in the *O*-alkylation of lactams. This was borne out by Meerwein *et al.*,<sup>42</sup> who arranged carbonyl compounds according to their capacity to undergo alkylation with oxonium salts as follows: lactams > acyclic amides > lactones > carboxylic esters > ketones > aldehydes.

## B. OTHER METHODS OF SYNTHESIS OF LACTIM ETHERS

An important method for the preparation of lactim ethers is the transformation of lactams to imidochlorides followed by treatment with alcohols. Thus, the reaction of caprolactam with phosphoryl chloride followed by methanol resulted in *O*-methylcaprolactim (2, R = Me)<sup>43</sup> (Scheme 2).



SCHEME 2

<sup>33</sup> R. G. Glushkov, V. A. Volskova, and O. Yu. Magidson, *Khim. Farm. Zh.* No. 9, 25 (1967).

<sup>34</sup> V. G. Granik and R. G. Glushkov, Witness of Authorship in the USSR No. 196876 (1966).

<sup>35</sup> V. G. Granik and R. G. Glushkov, *Khim. Farm. Zh.* No. 4, 16 (1967).

<sup>36</sup> V. G. Granik and R. G. Glushkov, Witness of Authorship in the USSR No. 196863 (1966).

<sup>37</sup> V. G. Granik and R. G. Glushkov, *Khim. Farm. Zh.* No. 5, 21 (1967).

<sup>38</sup> V. G. Granik and R. G. Glushkov, Witness of Authorship in the USSR No. 196864 (1966).

<sup>39</sup> V. G. Granik and R. G. Glushkov, *Khim. Farm. Zh.* No. 5, 16 (1967).

<sup>40</sup> V. G. Granik and R. G. Glushkov, *Khim. Farm. Zh.* No. 2, 16 (1968).

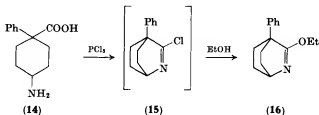
<sup>41</sup> V. G. Granik and R. G. Glushkov, *Zh. Org. Khim.* 724 (1968).

<sup>42</sup> H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert, and K. Wunderlich, *Ann.* **632**, 38 (1960).

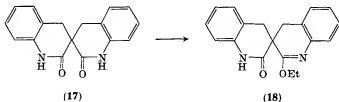
<sup>43</sup> R. G. Glushkov and O. Yu. Magidson, Witness of Authorship in the USSR No. 183757 (1965).



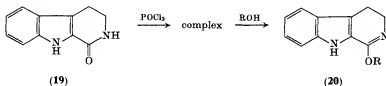
The interaction of 1-phenyl-4-aminocyclohexane 1-carboxylic acid (14) with  $\text{PCl}_5$  is accompanied by cyclization and formation of the imidochloride (15). Alcoholysis of the latter resulted in the lactim ether (16).<sup>44</sup>



Similarly, the reaction of the hydrocarbostyrylsipran (17) with  $\text{PCl}_5$  and  $\text{POCl}_3$  and alcoholysis of the intermediate yielded the lactim ether (18), obtained also as a by-product in the reduction of diethyl di(o-nitrobenzyl)malonate.<sup>45</sup>



Another example of the preparation of lactim ethers from lactams and phosphoryl chloride is the transformation of tetrahydro- $\beta$ -carbolin-1-one (19) to 1-alkoxy-3,4-dihydro- $\beta$ -carboline (20)<sup>46, 47</sup> (Scheme 3).



SCHEME 3

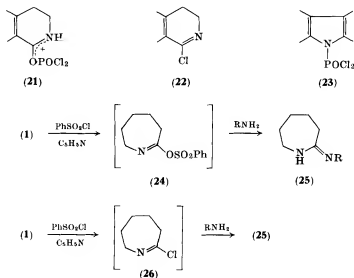
<sup>44</sup> C. F. Koelsch, *J. Org. Chem.* **25**, 164 (1960).

<sup>45</sup> H. Leuchs and H. V. Katinsky, *Ber.* **55**, 710 (1922).

<sup>46</sup> H. Henecka, R. Lorenz, and H. Timmler, German Patent 1,045,411 (1958); *Chem. Abstr.* **55**, 5543 (1961).

<sup>47</sup> R. A. Abramovitch and D. Spencer, *Advan. Heterocycl. Chem.* **3**, 117 (1964).

Though the structure of the intermediate complex has not been established, on the basis of the common properties of the carboxylic acid amides and lactams<sup>48-52</sup> it was suggested that the reaction of **19** with  $\text{POCl}_3$  results in compounds of type **21** or **22**. The indole part of the molecule, however, can also react with this reagent,<sup>33</sup> forming the *N*-dichlorophosphoryl derivatives (**23**). Simple lactams also react with benzenesulfonyl chloride. Short *et al.*<sup>53</sup> proposed a scheme, according to which caprolactam (**1**) and benzenesulfonyl chloride in the presence of pyridine yielded the unstable *O*-benzenesulfonyl derivative (**24**), which reacted with amines to afford cyclic amidines, such as **25**. Further investigation,<sup>54</sup> however, did not support their suggestion. Pyridinium benzenesulfonate was isolated in excellent yield from the reaction mixture, and a scheme involving the formation of the imido-chloride of caprolactam (**26**) was proposed.



<sup>48</sup> H. Bredereck, R. Gompper, K. Klemm, and H. Rempfer, *Ber.* **92**, 837 (1959).

<sup>49</sup> H. Bredereck, R. Gompper, and K. Klemm, *Ber.* **92**, 1456 (1959).

<sup>50</sup> H. Bredereck and K. Bredereck, *Ber.* **94**, 2278 (1961).

<sup>51</sup> Z. Arnold and A. Holy, *Collection Czech. Chem. Commun.* **27**, 2886 (1962).

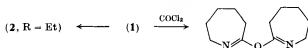
<sup>52</sup> K. Bredereck and S. Humburger, *Ber.* **99**, 3227 (1966).

<sup>53</sup> P. Oxley, D. A. Peak, and W. F. Short, *J. Chem. Soc.* 1618 (1948).

<sup>54</sup> R. G. Glushkov and E. S. Golovchinskaya, *Med. Prom. SSSR*, No. 1, 12 (1960).

The intermediate imidochloride (**26**) is highly susceptible to hydrolysis and all attempts to isolate it have failed.

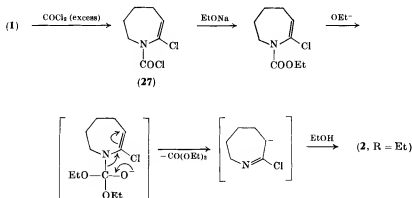
Presumably, the synthesis of lactim ethers from lactams and acylating agents, including phosgene and ethyl chloroformate, proceeds via intermediate imidochlorides<sup>55-57</sup> (Scheme 4).



SCHEME 4

The reaction between sulfonyl chlorides and cycloalkanone oximes in the presence of pyridine is followed by Beckmann rearrangement to the imidochlorides, which give the corresponding lactim ethers with alcohol.<sup>58</sup>

Tetenbaum<sup>59</sup> suggested Scheme 5 for the alcoholysis (NaOEt) of 1-chlorocarbonyl-2-chloro-4,5,6,7-tetrahydro-1*H*-azepine (**27**) to give caprolactim ethyl ether.



SCHEME 5

<sup>55</sup> K. Schmidt and P. Zutavern, German Patent 531,403 (1929); *Fortschr. Teefarbenfabrikation Industriezweige (Friedlaender)* **18**, 3052 (1933).

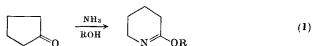
<sup>56</sup> W. Hechelhammer, German Patent 917,669 (1954); *Chem. Abstr.* **52**, 12898 (1958).

<sup>57</sup> W. Hechelhammer, German Patent 948,983 (1956); *Chem. Abstr.* **53**, 6088 (1959).

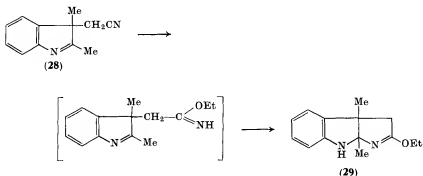
<sup>58</sup> K. Schmidt and P. Zutavern, German Patent 532,969 (1929); *Fortschr. Teefarbenfabrikation Industriezweige (Friedlaender)* **18**, 3050 (1933).

<sup>59</sup> M. T. Tetenbaum, *J. Org. Chem.* **31**, 4298 (1966).

A synthesis of lactim ethers based on the action of hydrazoic acid on cyclic ketones in the presence of alcohols has been developed [Eq. (1)].<sup>60</sup>

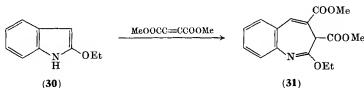


Individual methods for the synthesis of lactim ethers also depend on the nature of the starting materials, e.g., the transformation of 2,3-dimethyl-3-cyanomethylindolenine (**28**) to the tricyclic lactim ether (**29**) in the presence of sodium ethoxide<sup>61</sup> (Scheme 6).



SCHEME 6

Another example is the expansion of the heterocyclic ring of 2-ethoxyindole (**30**) to form the benzazepine (**31**).<sup>62</sup>



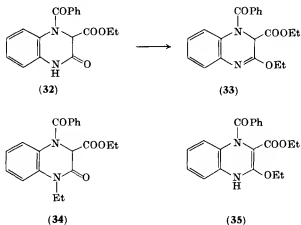
<sup>60</sup> K. Schmidt and P. Zutavern, German Patent 448,447 (1929); *Fortschr. Teefarbenfabrikation Industriezweige (Friedlaender)* **18**, 3048 (1933).

<sup>61</sup> M. Nakazaki, *Bull. Chem. Soc. Japan* **32**, 588 (1959).

<sup>62</sup> H. Plöninger and D. Wild, *Ber.* **99**, 3070 (1966).

### III. Chemical Properties and Reactions of Lactim Ethers

Lactim ethers are highly susceptible to nucleophilic reagents, being thus easily distinguished from other isomeric possibilities. Triethyloxonium fluoroborate with 3-carbethoxy-4-benzoyl-1,2,3,4-tetrahydroquinoxalin-2-one (32), for instance, gave a compound which may be represented by three isomeric structures (33–35). On infrared and PMR spectral evidence structure 35 could be excluded, but no choice between 33 and 34 could be made. Therefore the compound was hydrolyzed under very mild conditions ( $\text{H}_2\text{O}$ ,  $20^\circ\text{C}$ ), the initial lactam (32) being isolated quantitatively.<sup>63</sup> Other reactions confirmed the lactim ether structure (33) (see below).



The reactions of lactim ethers involving the lactim ether part may be classified into two groups.

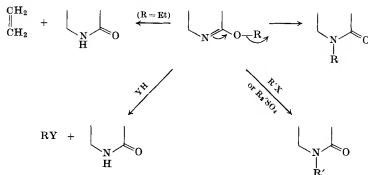
1. Reactions accompanied by alkyl-oxy fission, leading to lactam derivatives (Scheme 7).

2. Reactions involving loss of the entire alkoxy group (Scheme 8).

The thermal rearrangement of lactim ethers to *N*-alkyl lactams is a reaction of the first type. For example, 2-methoxy-3-oxoindolenine (36) undergoes thermal isomerization to *N*-methylizatin.<sup>64</sup> Benson and

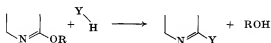
<sup>63</sup> V. G. Granik, Candidate's Dissertation, Moscow, Ordzhonikidze All-Union Chemical Pharmaceutical Scientific Research Institute, 1967.

<sup>64</sup> G. Heller, *Ber.* **52**, 437 (1919).



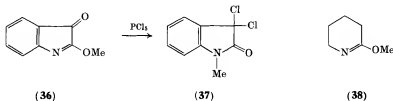
SCHEME 7

Cairns<sup>16</sup> have mentioned a similar rearrangement of *O*-methyl(ethyl) caprolactims (**2**, R = Me and R = Et) to *N*-methyl(ethyl) caprolactams (**3**, R = Me and R = Et), and a similar rearrangement takes place in



SCHEME 8

the transformation of **36** with  $\text{PCl}_5$  to *N*-methyl-3,3-dichloroxindole (**37**).<sup>65</sup> According to some authors,<sup>16, 66</sup> this reaction is characteristic



of lactim ethers, and is similar to the rearrangement of simple imino ethers.<sup>7</sup> More recently, however, Ralls and Eliger<sup>67</sup> showed that **2** (R = Et) is stable at 193°C, and on continued heating (21 hr., 273°C) it rearranges to **3** (R = Et) in negligible yield, the main product of the reaction, caprolactam (**1**), being obtained by elimination of ethylene. The authors proved that the rearrangement of **2** (R = Et) to **3** (R = Et)

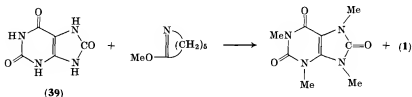
<sup>65</sup> A. Hantzsch, *Ber.* **54**, 1254 (1921).

<sup>66</sup> S. Petersen and E. Tietze, *Ber.* **90**, 909 (1957).

<sup>67</sup> J. W. Ralls and C. A. Eliger, *Chem. Ind. (London)*, 20 (1961).

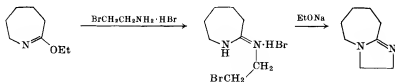
is caused by traces of dialkyl sulfate. Heating **2** ( $R = Et$ ) with diethyl sulfate yielded **3** ( $R = Et$ ) as the main product. The same is true of *O*-methylvalerolactim (**38**).<sup>67</sup> The need for dialkyl sulfate is in line with the earlier results of Benson and Cairns<sup>16</sup> (see Section II, A).

The alkylation of markedly acidic substances by lactim ethers is a reaction of the first type. Lactim ethers have been used as alkylating agents for imino compounds such as uric acid (**39**), xanthines, and hypoxanthine,<sup>68</sup> and for the esterification of organic acids.<sup>69</sup>



Reactions of the second type, especially those involving amino derivatives and compounds with active methylene groups, give rise to promising methods of heterocyclic synthesis.

The formation of amidines from lactim ethers and amines proceeds readily with high yields,<sup>8, 9, 16, 21, 70-76</sup> e.g., in the synthesis of imidazo-[1,2-*b*]azepine derivatives reported by Stolle *et al.*<sup>77</sup> (Scheme 9), and in the preparation of the pyrimido[1,2-*a*]-azepine derivative (Scheme 10).<sup>70</sup>



SCHEME 9

<sup>68</sup> W. Konz, U.S. Patent 2,767,182 (1956); *Chem. Abstr.* **51**, 8150 (1957).

<sup>69</sup> R. J. Leary, *Dissertation Abstr.* **17**, 1217 (1957); *Chem. Abstr.* **51**, 14763 (1957).

<sup>70</sup> R. G. Glushkov and O. Yu. Magidson, *Zh. Obshch. Khim.* **31**, 189 (1961).

<sup>71</sup> V. A. Plit and S. I. Burmistrov, *Ukr. Khim. Zh.* **24**, 467 (1958).

<sup>72</sup> A. Etienne and J. Correia, *Compt. Rend. C259*, 2660 (1964).

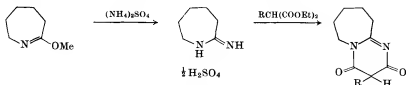
<sup>73</sup> French Patent 1,383,784 (1964).

<sup>74</sup> P. Schlack, U.S. Patent 2,356,622 (1944); *Chem. Abstr.* **39**, 1420 (1945).

<sup>75</sup> J. R. Geigy, French Patent 1,367,799 (1964); *Chem. Abstr.* **61**, 16055 (1964).

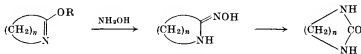
<sup>76</sup> G. Heller, *Ber.* **40**, 1296 (1907).

<sup>77</sup> R. Stolle, M. Merkle, and F. Hanusch, *J. Prakt. Chem.* **140**, 59 (1934).



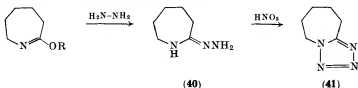
SCHEME 10

The reaction of lactim ethers with hydroxylamine results in lactam oximes.<sup>9, 72, 73, 78</sup> This reaction became important when the lactam oximes were found to undergo the Beckmann rearrangement with polyphosphoric acid, yielding polymethyleneureas<sup>79</sup> (Scheme 11).



SCHEME 11

The reaction of lactim ethers with hydrazine and its derivatives proceeds readily. The resulting compounds are highly reactive and can be used in different reactions involving the side chain and the cyclic nitrogen atom.<sup>5, 54, 76, 80-82</sup> For example, the treatment of caprolactam hydrazone (40) with nitrous acid results in pentamethylenetetrazole (41),<sup>54, 80, 81</sup> and the use of different lactim ethers gives other tetrazoles.<sup>32, 35</sup> The synthesis of polymethylenetetrazoles from lactim ethers and  $\text{HN}_3$ ,<sup>83</sup> and also<sup>84</sup> from  $\text{HN}_3$  and *O*-acyl lactims (or imidochlorides of lactams), obtained from lactams and sulfochlorides or phosphoryl chloride, may be mentioned.



<sup>78</sup> G. Heller, *Ber.* **49**, 2773 (1916).

<sup>79</sup> H. Behringer and H. Meir, *Ann.* **607**, 80 (1957).

<sup>80</sup> R. G. Glushkov and E. S. Golovchinskaya, *Zh. Prikl. Khim.* **32**, 920 (1959).

<sup>81</sup> R. Stolle, *Ber.* **63**, 1032 (1930).

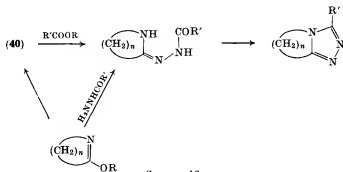
<sup>82</sup> K. Gatz, U.S. Patent 3,299,045 (1967); *Chem. Abstr.* **66**, 65407 (1967).

<sup>83</sup> A. G. Knoll, German Patent 521,870 (1929); *Fortschr. Teefarbenfabrikation Industriegewerbe (Friedlaender)* **17**, 2603 (1932).

<sup>84</sup> A. G. Knoll, German Patent 545,850 (1929); *Fortschr. Teefarbenfabrikation Industriegewerbe (Friedlaender)* **17**, 2605 (1932).

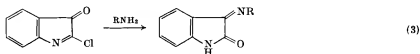
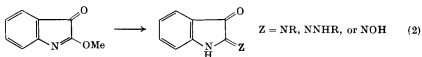


Polymethylenetriazoles may also be prepared from lactim ethers<sup>85-87</sup> (Scheme 12).



SCHEME 12

Amines and hydroxylamine and hydrazine derivatives react with **36** at the lactim ether group and not at the keto group<sup>76, 88</sup> [Eq. (2)]. By contrast, in the reaction between the imidochloride of isatin and tosylhydrazine (or aniline) the keto group at position 3 was found to be attacked and at the same time the imidochloride was transformed into the lactam<sup>89</sup> [Eq. (3)]. Thus it may be argued that, at least in the case of the isatin derivatives, the lactim ether function is more reactive than the imidochloride.



The reactions of lactim ethers with semicarbazides, thiosemicarbazides, and sulfonylhydrazides as a rule stop at the amidrazone stage.<sup>65</sup> It is interesting that with aliphatic imino ethers the reaction

<sup>85</sup> R. G. Glushkov and O. Yu. Magidson, *Zh. Obshch. Khim.* **30**, 649 (1960).

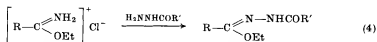
<sup>86</sup> S. Petersen, E. Tietze, and W. Wirth, U.S. Patent 2,852,525 (1958); *Chem. Abstr.* **53**, 6256 (1959).

<sup>87</sup> British Patent 825,514 (1959); *Chem. Abstr.* **55**, 7450 (1961).

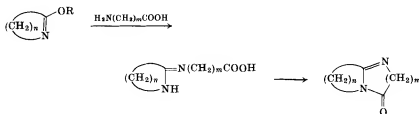
<sup>88</sup> J. Moriconi and J. J. Murray, *J. Org. Chem.* **29**, 3577 (1964).

<sup>89</sup> R. K. Callow and E. Hope, *J. Chem. Soc.* 1191 (1929).

follows a different course, with cleavage of the C=N bond and evolution of ammonia<sup>90-92</sup> [Eq. (4)].

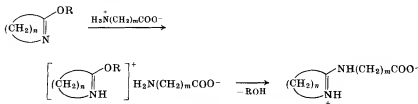


The reaction of lactim ethers with amino acids has been studied in detail.<sup>21, 23, 93</sup> These reactions proceed readily, resulting in the substituted amidino acids. Their cyclization yields fused dihydropyrimidinones or imidazolinones (Scheme 13). The cyclization of the aliphatic amidino acids requires drastic conditions, whereas aromatic and heterocyclic amidino acids react under mild conditions, perhaps due to the formation of the new aromatic ring which stabilizes the resulting structure.



SCHEME 13

Korosi<sup>94</sup> proposed that the initial amidino acid is formed as shown in Scheme 14. According to this scheme the reaction is initiated by proton transfer from the amino acid to the lactim ether, being easier with aromatic and heterocyclic than with aliphatic amino acids. The



SCHEME 14

<sup>90</sup> H. Weidinger and J. Kranz, *Ber.* **96**, 1049 (1963).

<sup>91</sup> H. Weidinger and J. Kranz, *Ber.* **96**, 1059 (1963).

<sup>92</sup> H. Weidinger and J. Kranz, *Ber.* **96**, 1064 (1963).

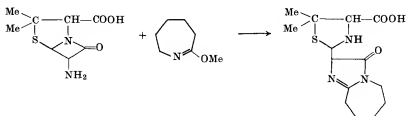
<sup>93</sup> G. Heller and W. Benade, *Ber.* **55**, 1011 (1922).

<sup>94</sup> J. Korosi, *J. Prakt. Chem.* **23**, 212 (1964).

protonation of the lactim nitrogen increases the electrophilic nature of the neighboring carbon atom and promotes the nucleophilic replacement. Thus the reaction between lactim ethers and amines depends on the basicity of the initial amine and also on the possibility of protonation of the lactim nitrogen.

The reaction of a lactim ether with an amino acid ester yields the corresponding amidino acid ester.<sup>95</sup> The principal factor determining the rate of this reaction is, probably, the basicity of the amino group. For instance, the condensation of a lactim ether with an ester of aminocrotonic acid appears either to fail<sup>21, 95</sup> or to proceed in comparatively low yields.<sup>70</sup>

The interaction of **2** (R = Me) with 6-aminopenicillanic acid took place with opening of the  $\beta$ -lactam ring followed by cyclization of the penicilloinic acid derivative (**20**) that was formed<sup>96</sup> (Scheme 15).



SCHEME 15

The readiness of amidine formation in reactions of lactim ethers with amines has been used in the synthesis of 8,9-polymethylenepurines.<sup>97</sup> Attempts to condense **2** (R = Me) with uramil and 1,3-dimethyl-4,5-diaminouracil failed.<sup>97</sup> Lactim ethers were also found not to react with derivatives of 5-aminouracil, probably due to the low basicity of the latter.<sup>97</sup>

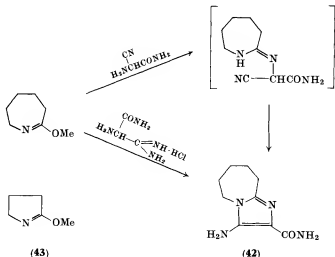
1,2-Polymethylene derivatives of 4-carboxamido-5-aminoimidazoles, from which 8,9-polymethylenepurines were derived, were synthesized by the condensation of lactim ethers with  $\alpha$ -amino- $\alpha$ -cyanoacetamide. In spite of the presence of an active methine group, the reaction proceeded exclusively on the amino group, as shown by the physicochemical properties of the resulting compounds and, in the

<sup>95</sup> A. Etienne, A. Le Berre, and C. Renault, *Compt. Rend.* **C262**, 365 (1966).

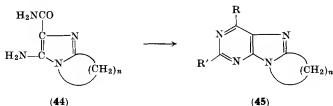
<sup>96</sup> R. G. Glushkov, *Zh. Obshch. Khim.* **36**, 948 (1966).

<sup>97</sup> R. G. Glushkov and O. Yu. Magidson, *Zh. Obshch. Khim.* **31**, 1173 (1961).

case of **2** ( $R = \text{Me}$ ) was confirmed by an unambiguous synthesis of 1,2-pentamethylene-4-carboxamido-5-aminoimidazole (**42**).<sup>97</sup> Exten-

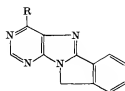


sion of this reaction to *O*-methylbutyrolactim (**43**) and *O*-methylvalerolactim (**38**) showed the necessity for increasing the electrophilic character of the lactim carbon.<sup>98</sup> This was achieved by carrying out the reaction in alcohol containing hydrogen chloride. Thus the reaction of lactim ethers with  $\alpha$ -amino- $\alpha$ -cyanoacetamide offers a synthesis of polymethyleneimidazoles (**44**) and 8,9-polymethylene-purines (**45**) therefrom. The general nature of this reaction was confirmed by more complex examples, for instance, by analogous reactions of lactim ethers containing additional heteroatoms<sup>32, 35, 99</sup> (forming compounds **46**), and of 1-ethoxyisindolenine<sup>24</sup> (leading to **47**).



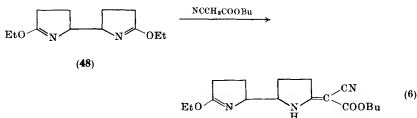
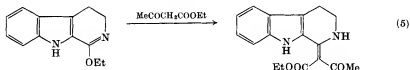
<sup>98</sup> R. G. Glushkov and O. Yu. Magidson, *Zh. Obshch. Khim.* **31**, 1906 (1961).

<sup>99</sup> R. G. Glushkov and A. R. Todd, *Khim. Geterotsikl. Soedin*, No. 3, 433 (1968).

(46)  $X = O, S, NR'$ 

(47)

A new carbon-carbon bond is formed during the reaction of lactim ethers with compounds containing active methylene groups, such as malonic ester and its derivatives, acetylacetone, barbituric acid, rhodanine, nitromethane, and oxindole.<sup>8, 9, 33, 100-102</sup> Examples are the condensation of the lactim ether of tetrahydro- $\beta$ -carbolinone with acetoacetic ester<sup>103</sup> [Eq. (5)] and the condensation of the bislactim ether of 2,2'-dipyrrolidine-5,5'-dione (48) with butyl cyanoacetate<sup>26</sup> [Eq. (6)]. Another instance is the reaction of 2 ( $R = Me$ ) with 2-phenyloxazolin-5-one, to give 3,4-pentamethyleneimidazoles (49) via the intermediate 4-(homopiperid-2-ylene)oxazolin-5-one (50)<sup>104</sup> (Scheme 16).



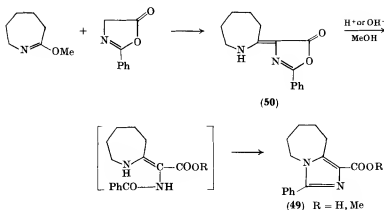
<sup>100</sup> F. Bohlmann and N. Ottawa, *Abhandl. Braunschweig Wiss. Ges.* **9**, 177 (1957); *Chem. Abstr.* **52**, 10880 (1961).

<sup>101</sup> S. Petersen, German Patent 863,056 (1953); *Chem. Zentr.* 8416 (1953).

<sup>102</sup> A. Wahl and P. Bagard, *Compt. Rend.* **156**, 900 (1913).

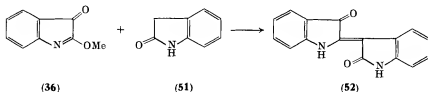
<sup>103</sup> H. Henecka, R. Lorenz, and H. Timmler, German Patent 1,044,818 (1958); *Chem. Abstr.* **55**, 3622 (1961).

<sup>104</sup> R. G. Glushkov and O. Yu. Magidson, *Zh. Obshch. Khim.* **30**, 1855 (1960).

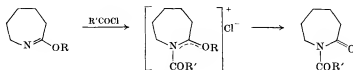


SCHEME 16

The isatin lactim ether (36) reacts with oxindole (51) in anhydrous medium (benzene, acetic anhydride) containing sulfuric acid to give indirubin (52).<sup>102</sup>



Sehring and Konz reported in 1956 that the reaction of lactim ethers with acid chlorides results in *O*-acyl lactims.<sup>105</sup> In 1965, however, Stolle and Griehl<sup>106</sup> stated that the earlier work was erroneous; *N*-acyl lactams were formed (Scheme 17), and this certainly seems more likely.

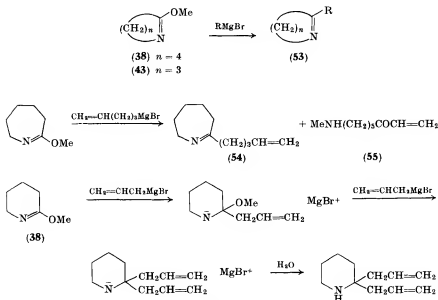


SCHEME 17

<sup>105</sup> R. Sehring and W. Konz, German Patent 949,057 (1956); *Chem. Abstr.* **53**, 6275 (1959).

<sup>106</sup> B. Stoll and W. Griehl, *Helv. Chim. Acta* **48**, 1805 (1965).

A number of papers have been devoted to the reactions of lactim ethers with Grignard reagents.<sup>72, 73, 107-112</sup> This reaction depends on the size of the lactam ring. Thus, whereas **38** and **43** yielded bases (**53**), *O*-methylcaprolactim gave, besides similar bases (e.g., **54**), *N*-methylaminoketones (e.g., **55**), formed evidently, by the transformation of **2** to **3** followed by reaction with the Grignard reagent.<sup>109</sup> Normally, when in RMgX, R equals simple alkyls or aryls, the Grignard reagent reacts only once to substitute its alkyl (aryl) group for the alkoxy group of the lactim ether. An instance of further reaction with a second mole of Grignard reagent is the reaction of **38** with allyl magnesium bromide<sup>112</sup> to yield the derivative shown (Scheme 18). Allyl magnesium bromide is known to add to the double bond of 2-propyl-3,4,5,6-tetrahydropyridine (**56**) with formation of 2-propyl-2-allylpiperidine (**57**).



SCHEME 18

<sup>107</sup> V. Dudek and O. Li-Kuan, *Collection Czech. Chem. Commun.* **30**, 2472 (1965).

<sup>108</sup> H. Booth, A. W. Johnson, and F. Johnson, *J. Chem. Soc.* 98 (1962).

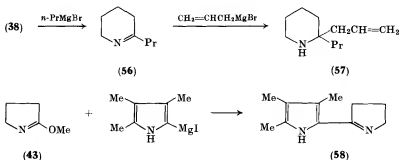
<sup>109</sup> O. Červinka, *Collection Czech. Chem. Commun.* **24**, 1146 (1959).

<sup>110</sup> R. Lukeš and O. Červinka, *Chem. Listy* **52**, 83 (1958).

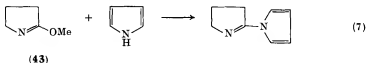
<sup>111</sup> R. Lukeš and O. Červinka, *Collection Czech. Chem. Commun.* **24**, 1846 (1959).

<sup>112</sup> R. Lukeš and M. Černý, *Collection Czech. Chem. Commun.* **26**, 2886 (1961).

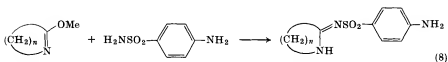
An interesting example of this reaction is in the synthesis of 2,2'-pyrrolylpyrrolines, such as **58**, where the use of a magnesium derivative of the pyrrole favors the condensation of **43** with the



$\alpha$ -position of the pyrrole ring. When pyrrole itself was used, condensation took place at the pyrrole nitrogen<sup>113</sup> [Eq. (7)].



Sulfonamides also condense with lactim ethers. It has been reported<sup>114</sup> that in one case a lactim ether reacted with a sulfonamide group even in the presence of an aromatic amino group [Eq. (8)].

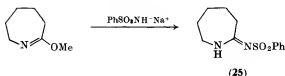


*O*-Methylcaprolactim with ammonium benzenesulfonate yielded the corresponding amidine salt, and with the sodium salt of benzenesulfonamide it gave the benzenesulfonyl derivative of caprolactamidine (**25**).<sup>11</sup>

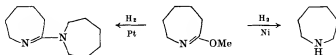
<sup>113</sup> R. Bonnett, K. S. Chen, and A. G. Gale, *Can. J. Chem.* **42**, 1073 (1964).

<sup>114</sup> K. Mailer, H. Baumann, and D. Leuchs, *Auslegeschriften der Patentanmeldungen des Deutschen Patentamtes München (D.A.S.)*, No. 1,085,160 (1960); *Chem. Zentr.* **132**, 4524 (1961).





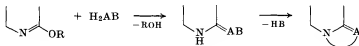
The reduction of lactams proceeds with difficulty, generally requiring the use of lithium aluminum hydride. Lactim ethers, however, undergo facile reduction, providing a good method for the preparation of cyclic imines from lactams via the ethers.<sup>16, 72, 109</sup> Benson and Cairns reported<sup>16</sup> that hydrogenation of **2** ( $R = \text{Me}$  or  $\text{Et}$ ) with Raney nickel, ruthenium oxide, and barium-copper chromite catalysts resulted in good yields of hexamethylenimine. The use of a platinum



SCHEME 19

catalyst yielded amidines (Scheme 19). Piperidine<sup>109</sup> and pyrrolidine<sup>72</sup> can be prepared by catalytic hydrogenation of the appropriate lactim ether (**38**, **43**) over platinum. Lithium aluminum hydride may, of course, also be used.

Heterocyclic syntheses so far considered have involved the imino ether function only, with the new heterocyclic rings being produced by displacement of the ether group followed by cyclization to the

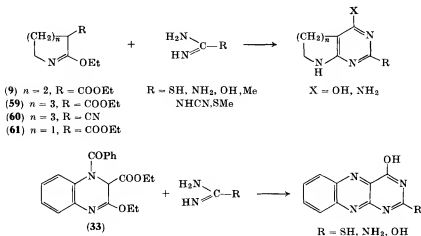


SCHEME 20

lactim nitrogen atom (Scheme 20). Recently, investigations have been carried out on lactim ethers with extra functional groups.<sup>25, 36-41, 115</sup> The first heterocyclic synthesis from such a compound was the reaction between the lactim ether of 3-carbethoxypiperidone-2 (**9**) and thiourea in the presence of sodium ethoxide.<sup>25</sup> Further investigations have been conducted with **9**, **33**, and the lactim ethers of 3-cyanocaprolactam, 3-carbethoxycaprolactam, and 3-carbethoxypyrrolidin-2-one (**59-61**)<sup>38, 39, 41, 115</sup> (Scheme 21). The reaction was shown to

<sup>115</sup> B. M. Pyatin and R. G. Glushkov, *Khim. Farm. Zh.* No. 9, 17 (1968).

be a general one for the synthesis of fused pyrimidines, but the efficiency of the process depends on the nature of the lactim ethers and the amidine components. The use of guanidine and thiourea as amidine components always gave good results, but in the condensation of **33**, **60**, and **61** with urea, the fused uracils were obtained in poor yield, whereas a similar reaction with **9** gave a satisfactory yield of 2,4-dihydropiperido[2,3-*d*]pyrimidine, comparable to that obtained in the reaction of **9** with acetamidine.



SCHEME 21

Other amidine components are arranged according to their reactivity: guanidine  $\simeq$  thiourea  $>$  dicyandiamide  $>$  acetamidine  $>$  *S*-methylisothiurea  $>$  urea.

Except for the abnormally low yield with *S*-methylisothiurea, the reactivity of the amidine components is similar to that in the usual pyrimidine cyclizations.<sup>116-119</sup> The condensation of lactim ethers derived from 3-carbethoxylactams with amidines depends on the stability of the reagents.<sup>120</sup> Lactim ethers, just as aliphatic imino ethers, are labile to acidic and alkaline media, hence the yields depend on the rate of cyclization. With basic or enolizable amidines, the

<sup>116</sup> W. Wamhoff and F. Korte, *Ber.* **99**, 872 (1966).

<sup>117</sup> K. A. Chkhikvadze and O. Yu. Magidson, *Zh. Obshch. Khim.* **34**, 2577 (1966).

<sup>118</sup> A. Schrage and G. H. Hitching, *J. Org. Chem.* **16**, 1153 (1951).

<sup>119</sup> J. D. Fissekis, A. Myles, and G. B. Brown, *J. Org. Chem.* **29**, 2670 (1964).

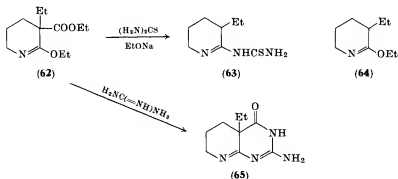
<sup>120</sup> R. Ya. Levina and F. K. Velichko, *Usp. Khim.* **29**, 929 (1960).

pyrimidine cyclization predominated. With other amidines, alcoholysis to lactams occurred.<sup>121</sup>

The lactim ether (59) derived from 3-carbethoxycaprolactam condensed with urea to give a fused uracil in low yield, but the analogous reaction with the cyano derivative (60) failed.

The use of bifunctional lactim ethers in the above reaction forms the new heterocyclic system pyrimido[4,5-*b*]tetrahydroazepine,<sup>36, 37</sup> and is a new method for the synthesis of alloxazines,<sup>42</sup> 7*H*-5,6-dihydro-pyrrolo[2,3-*d*]pyrimidines,<sup>38, 39</sup> and 8*H*-piperido[2,3-*d*]pyrimidines<sup>25, 115</sup> (Scheme 21).

Condensation of the lactim ether (62) of 3-ethyl-3-carbethoxy-2-piperidone with thiourea, guanidine, and other amidine components gave the fused piperidino[2,3-*d*]pyrimidines with an angular ethyl group in the 3-position (65), these are cyclic analogs of the biologically active 5,5-disubstituted barbiturates.<sup>115</sup> However, 62 did not condense with thiourea and with an equimolecular amount of sodium ethoxide, whereas an excess of ethoxide gave only *N*-(3-ethyl-3,4,5,6-tetrahydro-2-pyridyl)thiourea (63). The loss of the carbethoxy group is probably due to alcoholysis, with formation of diethyl carbonate, as in the reaction of cyanoacetates with urea.<sup>122, 123</sup>



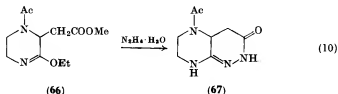
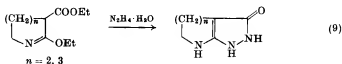
The carbethoxy group in 62 increases the partial positive charge on the "lactim" carbon atom and makes it more reactive than in the lactim ether (64) of 3-ethyl-2-piperidone. Probably the lactim carbon is first attacked by thiourea; excess of sodium ethoxide promotes the

<sup>121</sup> W. Heldt, *J. Am. Chem. Soc.* **80**, 5880 (1958).

<sup>122</sup> A. C. Cope and E. M. Hancock, *J. Am. Chem. Soc.* **61**, 776 (1939).

<sup>123</sup> A. C. Cope and E. M. Hancock, *J. Am. Chem. Soc.* **61**, 353 (1939).

reaction by ionization of the thiourea. The reaction of **63** with a stronger base such as guanidine gave 2-amino-10-ethyl-4-hydroxy-4,5,6,7,8,10-hexahydropyrido[2,3-*d*]pyrimidine (**65**); the yield was lower than in the analogous reaction of **9** due to the nonaromatic pyrimidine ring in **65**. The importance of aromatization is confirmed by the failure to condense the lactim ether (**66**) of 3-carbomethoxymethyl-4-acetyl-2-piperazinone with amidines.<sup>40</sup> The ether (**62**) does not react with urea, due perhaps to the lesser enolization of the latter as compared with thiourea.<sup>113</sup> The decreased reactivity of the lactim ether group of **62** as compared with **9** may be due to the electron-donating effect of the 3-alkyl group. The lower reactivity of **62** as compared with **9**, **33**, **60**, and **61** is confirmed by its partial stability under the reaction conditions.<sup>115</sup> The reaction of bifunctional lactim ethers with amidines has been extended to other bidentate amine components, leading to numerous heterocyclic syntheses; e.g., lactim ethers with hydrazine hydrate give fused pyrazoles<sup>25, 37</sup> [Eq. (9)] and pyridazines<sup>40</sup> [Eq. (10)]. The "amidine" structure of **67** was proved by infrared and NMR spectra.



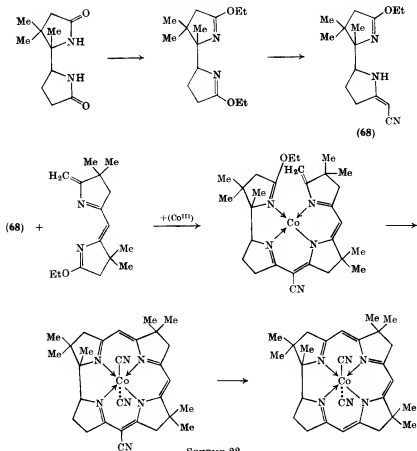
Lactim ethers have been used for the synthesis of complex organic molecules such as corrins,<sup>124-127</sup> e.g., racemic dicyanocobalt(III) 1,2,2,7,7,12,12-heptamethylcorrin<sup>125</sup> (Scheme 22).

<sup>124</sup> E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, J. Felner, H. P. Gribo, H. Gschwend, E. F. Meyer, M. Pesaro, and R. S. Scheffold, *Angew. Chem.* **76**, 393 (1964).

<sup>125</sup> J. Felner, A. Fischli, A. Wick, M. Pesaro, D. Bormann, E. L. Winnacker, and A. Eschenmoser, *Angew. Chem.* **79**, 863 (1967).

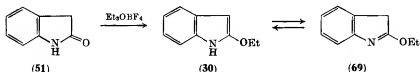
<sup>126</sup> A. Fischli and A. Eschenmoser, *Angew. Chem.* **79**, 865 (1967).

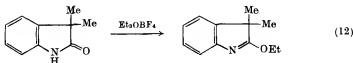
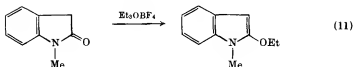
<sup>127</sup> D. Bormann, A. Fischli, R. Keesse, and A. Eschenmoser, *Angew. Chem.* **79**, 867 (1967).



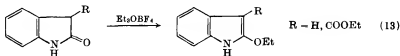
SCHEME 22

The alkylation of oxindole (**51**) and its derivatives by triethyloxonium fluoroborate is of special interest. Harley-Mason and Leeney<sup>22</sup> showed that **30** was the product, which isomerized to the lactim ether (**69**) of **51** when sublimed. Heating **69** above its melting point yielded **30** again. 1-Methyl-2-ethoxyindole and the lactim ether of 3,3-dimethylindolenine were used as models [Eqs. (11) and (12)] in an NMR





and infrared study of the products. Both **30** and **69** are present at equilibrium in chloroform, with **69** predominating. Another attempt<sup>33</sup> to obtain **69** and the lactim ether of 3-carbethoxyoxindole gave only indole derivatives [Eq. (13)].



The condensation of **30** (via **69**) with  $\alpha$ -amino- $\alpha$ -cyano-acetamide in alcohol, using hydrogen chloride as catalyst, probably gave 2-carbamido-3-aminopyrrolo[2,3-*b*]indole (**70**) (Scheme 23); a possible "normal" reaction product<sup>128</sup> would possess the structure 2-carbamido-3-aminoimidazo[1,2-*a*]indoline (**71**).

Some lactim ethers are sufficiently stable to undergo complex transformations, e.g., the isomerization of **72** with retention of the lactim ether function<sup>27</sup> (Scheme 24).

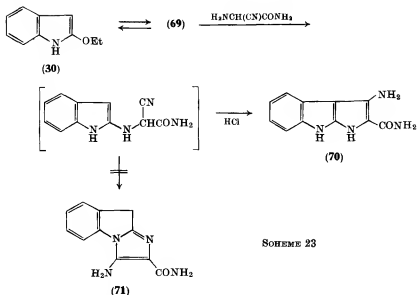
Finally, it should be noted that the investigations of Bredereck<sup>50, 129</sup> and Meerwein *et al.*<sup>130, 131</sup> on the preparation of lactam acetals have significantly widened the scope of utility of *O*-alkyl derivatives of lactams, and have extended some of the reactions of lactim ethers, discussed in this review, to *N*-substituted lactam acetals.

<sup>128</sup> W. J. Fanshawe, V. J. Bauer, E. F. Ullman, and S. R. Safir, *J. Org. Chem.* **29**, 308 (1964).

<sup>129</sup> H. Bredereck, F. Effenberger, and H. P. Beyerlin, *Ber.* **97**, 3081 (1964).

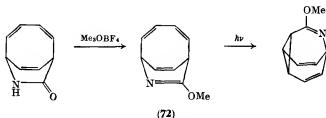
<sup>130</sup> H. Meerwein, W. Florian, N. Schon, and G. Stopp, *Ann.* **641**, 1 (1961).

<sup>131</sup> H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodt, and J. Spille, *Ber.* **89**, 2060 (1956).



SCHEME 23

Thus the application of lactim ethers in organic synthesis is of practical and theoretical importance. Numerous heterocycles, including new heterocyclic systems interesting both from biological and chemical standpoints have been obtained. The wide choice of readily available starting materials makes the use of lactim ethers profitable in synthetic organic chemistry.



SCHEME 24

# Electrolysis of *N*-Heterocyclic Compounds

HENNING LUND

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## I. Introduction

In this chapter the electrolysis of *N*-heterocyclic compounds is discussed; the emphasis will be laid on preparative electrolysis, but polarographic results will also be mentioned to supplement the discussion and to suggest further use of preparative electrolysis. Electro-



lysis at a controlled potential will be the main subject, and only a brief survey of "classical" reactions is included as such reactions are treated in earlier books<sup>1-3</sup> and reviews.<sup>4-6</sup> The theoretical and practical background for electrolysis<sup>7,8</sup> is discussed only to the extent necessary for the organic chemist to acquire a working knowledge of the subject.

A presentation of electroanalytical methods such as classical polarography<sup>9-11</sup> and cyclic voltammetry<sup>12</sup> may be found in different monographs; an excellent discussion of electrochemical properties of heterocyclic compounds in solution,<sup>13</sup> published a few years ago, is very relevant to the present chapter and covers most of the background needed.

The electrolytic method of reducing and oxidizing organic molecules has many inherent advantages and disadvantages. The most obvious advantage of the electrolytic method is that it presents the possibility of controlling over a wide range the activity of the reagent, the electron, by proper choice of the electrode potential. The electrode potential is the potential difference across the electrical double layer, and the main part of this potential drop occurs within a distance of a few

<sup>1</sup> F. Fichter, "Organische Elektrochemie." Steinkopff, Dresden und Leipzig, 1942.

<sup>2</sup> M. J. Allen, "Organic Electrode Processes." Chapman & Hall, London, 1958.

<sup>3</sup> A. P. Tomilov, S. G. Mairanovskii, M. Ya. Fioshin, and V. A. Smirnov, *Elektrokhimiya Organicheskikh Soedinenii*, "Khimiya," Leningrad, 1968.

<sup>4</sup> S. Swann, *Trans. Electrochem. Soc.* **69**, 53 (1936), **77**, 40 (1940), **88**, 18 (1945).

<sup>5</sup> F. D. Popp and H. P. Schultz, *Chem. Rev.* **62**, 19 (1962).

<sup>6</sup> C. L. Perrin, *Prog. Phys. Org. Chem.* **3**, 165-316 (1965).

<sup>7</sup> B. E. Conway, "Theory and Principles of Electrode Processes." Ronald Press, New York, 1965.

<sup>8</sup> R. A. Marcus, *Discussions Faraday. Soc.* **45**, 7 (1968).

<sup>9</sup> I. M. Kolthoff and J. J. Lingane, "Polarography," 2nd ed. Interscience, New York, 1952.

<sup>10</sup> J. Heyrovský and J. Kuta, "Grundlagen der Polarographie." Akademie Verlag, Berlin, 1965.

<sup>11</sup> L. Meites, "Polarographic Techniques," 2nd ed. Wiley (Interscience), New York, 1965.

<sup>12</sup> R. N. Adams, "Electrochemistry at Solid Electrodes." Dekker, New York, 1969.

<sup>13</sup> J. Volke, in "Physical Methods in Heterocyclic Chemistry," Vol. 1. (A. R. Katritzky, ed.), Vol. 1. Academic Press, New York, 1963.

Ångströms from the electrode surface; the electrical gradient near the electrode is thus of the order of  $10^7$ – $10^8$  volts/cm.<sup>14</sup>

Another advantage is that the transfer of electrons can occur at low temperature and at a chosen pH, so temperature- and acid- or base-sensitive compounds, such as many biologically active molecules, can be reduced or oxidized under mild and well-defined conditions.

Compared with reactions brought about by chemical reagents, the electrolytic method is favored by the absence of these reagents and the reaction products thereof, which facilitates the isolation of the product, and may reduce the extent of side reactions and make the development of a continuous process easier. The electrolytic process is also inherently easy to control automatically.

An obvious disadvantage of the method is that the reaction of one mole of a substance requires  $n \times 96,500$  coulombs, where  $n$  is the number of electrons in the electrode reaction. As high currents can be employed when properly designed apparatus and well-chosen conditions are used, however, this is not a serious disadvantage. Furthermore, the electron is a very inexpensive reagent.

A more serious limitation in the use of electrolytic reactions may be caused by the necessity of employing a medium capable of conducting the electrical current. From the point of view of electrolytic reactions water is a suitable solvent, but the problem of solubility of the reacting substances often requires an organic solvent or a mixed solvent as medium. In some cases, the use of "hydrotropic" solvents,<sup>15</sup> such as a strong aqueous solution of a tetraalkylammonium toluenesulfonate, may be advantageous. In aprotic solutions the low concentration of protons must be taken into consideration by adding suitable proton donors, unless the scarcity of protons is important for the formation of the desired product which might not survive in a proton-rich medium. This has, for example, been utilized in the electrolytic generation of strong bases to promote Wittig and similar reactions.<sup>16</sup>

## II. Theory

The electrolysis of an organic compound involves one or more steps in which electrons are transferred to or from the electrode [the

<sup>14</sup> G. J. Hoijtink, *Rec. Trav. Chim.* **76**, 885 (1957).

<sup>15</sup> R. M. McKee, *Ind. Eng. Chem.* **38**, 382 (1946).

<sup>16</sup> P. E. Iversen and H. Lund, *Tetrahedron Letters* 3523 (1969).

electrochemical step(s)] and some chemical steps before and/or after the electrochemical steps.

The reduction potential of a compound depends on the energy of the lowest vacant molecular orbital, whereas the oxidation potential is dependent on the energy of the highest occupied orbital. If the electron-transfer reaction is fast, i.e., a reversible reaction, the reduction potentials of a series of compounds may be evaluated theoretically with some success when complicating factors, such as solvation energy, are constant or absent. Quantum mechanical calculation of polarographic half-wave potentials of azaheteroaromatic compounds have been performed using different approximations.<sup>17-19</sup>

The mechanism of the electron-transfer reaction is not well understood; questions concerning how close an approach of the substrate to the electrode is necessary and the role of orientation, adsorption, polarizability, and solvent molecules in the process, are discussed presently.

In many cases the electron-exchange reaction and coupled reactions are slow at the potential at which the transport of electrons to and from the electrode is equal, i.e., the "reversible" potential, and it is then necessary to apply an extra potential, an overvoltage, to obtain a reasonable rate of reaction. The overvoltage is dependent on many parameters, and it has not been possible to predict it on theoretical grounds. The potentials to be used in electrolysis may thus be found empirically, e.g., from current-voltage curves of micro-electrodes.

Electrode reactions may be divided into two main types (A and B) depending on whether the electron transfer occurs directly between the electrode and the substrate (A) or whether the electron is transferred to (or from) another species which then reacts with the substrate (B).

#### A. DIRECT ELECTRON-TRANSFER REACTIONS

Reactions following the direct electron-transfer mechanism may be classified according to whether the potential necessary for the electron transfer can be reached within the decomposition potentials of the medium or not. In the former case (A1) a reaction at controlled

<sup>17</sup> G. Anthoine, J. Nasielski, E. Vander Donckt, and N. Vanlaetern, *Bull. Soc. Chim. Belges* **76**, 230 (1967).

<sup>18</sup> B. J. Tabner and J. R. Yandle, *J. Chem. Soc. A* **381** (1968).

<sup>19</sup> D. van der Meer and D. Feil, *Rec. Trav. Chim.* **87**, 746 (1968).

electrode potential can occur with 100% current efficiency because the potential is kept at a value where only the desired electrode process can take place; in the latter type (A2) a certain part of the current is always consumed in the decomposition of the medium and the current yield depends on how well the substrate competes with the medium for the electrons.

Reactions of the A1 type have been investigated in more detail than the others. Most of the reactions treated in this chapter are of this type. On the basis of results obtained by electroanalytical methods (e.g., polarography<sup>9-11</sup>, cyclic voltammetry<sup>12, 20</sup>) meaningful predictions can be made about the optimum conditions for an electrolysis, e.g., the dependence of the electrode potential on experimental conditions, and the number of electrons participating in the electrode reaction can be found. This technique will be discussed in more detail later.

Many of the "classical" electrolytic reactions occur at a potential which is either more negative (reduction) or more positive (oxidation) than the decomposition potentials of the media. The mechanism of such reactions must be investigated in each case, but it can usually be classified as one of the following three cases: (1) a direct electron transfer from electrode to substrate (A2), (2) a formation of "solvated electrons" which, in turn, reduce the substrate (B1), or (3) a formation of an active species in the electrochemical step (adsorbed hydrogen, active metals, hydrogen peroxide, hydroxyl radicals, halogens, etc.) which reacts chemically with the substrate (B2).

In hydroxylic media the electrode reactions involve probably a direct electron transfer between electrode and substrate when the electrode material has a high overvoltage and a low catalytic effect; such reactions are not, in principle, different from those treated as A1, only the potential necessary to cause the electron transfer is (numerically) higher than that at which the medium is decomposed.

The current-voltage curve of the decomposition reaction of the medium can be described by the well-known Tafel equation,  $E = a + b \log I$ , where  $a$  and  $b$  are constants and  $I$  is the current density (amps/cm<sup>2</sup>);  $a$  is dependent on the electrode material, and  $b$  is determined by the mechanism of the electrode reaction.

If  $E_1$  (Fig. 1) is the potential at which the decomposition of the medium starts, and  $E_2$  ( $|E_2| > |E_1|$ ) is the potential the substrate

<sup>20</sup> R. S. Nicholson and I. Shain, *Anal. Chem.* **36**, 706 (1964).

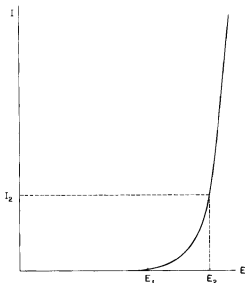


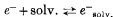
FIG. 1. Schematic representation of the connection between electrode potential  $E$  and current density  $I$  in the decomposition reaction of the medium. Hydrogen (oxygen) evolution starts at  $E_1$ ; if the substrate requires for the electrochemical step a potential (numerically) higher than  $E_2$ , transfer of electrons to the substrate becomes appreciable only if  $I > I_2$ .

requires for the transfer of electrons, it is only possible to obtain that potential when a certain current density  $I_2$  is reached. At potentials numerically higher than  $E_2$  (and thus current densities higher than  $I_2$ ) the reduction (oxidation) of the medium and of the substrate competes. The outcome of this competition, the current efficiency, is determined by several factors such as electrode material, specific adsorption of the substrate, concentration of the substrate, and composition of the medium. Generally, it can be said that an electrode material with high overvoltage, a high concentration of the substrate, and a high current density (but not higher than the effective limiting current of the substrate) will favor a high current efficiency.

The reaction is, however, more complicated than suggested above; one reason is that the presence of a high concentration of substrate changes the medium considerably, especially near the electrode surface if specific adsorption of the substrate, which is often of importance for the reaction, occurs.

## B. INDIRECT ELECTROCHEMICAL REACTIONS

Among the electrolytically produced reagents which have been considered to be operating is the solvated electron. It may be formed in reductions in nonaqueous media such as ammonia,<sup>21</sup> ethylenediamine<sup>22, 23</sup>, methylamine,<sup>24</sup> polyethylene glycol dimethyl ether,<sup>25</sup> and ethanol containing hexamethylphosphoramide,<sup>26</sup> at electrodes with high hydrogen overvoltage, and with tetraalkylammonium or lithium ions as supporting electrolyte. The reaction can be written as



where S is the substrate.

The standard potential of the solvated electron is about  $-2.6$  volts (NHE)<sup>27</sup> and solvated electrons can only be formed in the absence of more easily reducible substrates.

Whereas the reductions involving solvated electrons stand between the purely electrochemical and the indirect reductions, the reactions involving the formation of adsorbed hydrogen, amalgams, hydroxyl radicals, halogens, etc., are clearly indirect electrolytic reactions.

Electrocatalytic reduction may be important at electrodes with low hydrogen overvoltage and high catalytic activity, and its mechanism is closely related to the mechanism of the hydrogen evolution.

Recent investigations<sup>28</sup> have shown that two independent paths are accessible for the electrocatalytic reduction of, e.g., acetone in  $6\text{ }N\text{ H}_2\text{SO}_4$  at a platinized platinum electrode; one leads to propane and

<sup>21</sup> A. J. Birch, *Nature* **158**, 60 (1946).

<sup>22</sup> H. W. Sternberg, E. M. Kaiser, and R. F. Lambert, *J. Electrochem. Soc.* **110**, 425 (1963).

<sup>23</sup> H. W. Sternberg, R. E. Markby, J. Wender, and D. M. Mohilner, *J. Electrochem. Soc.* **111**, 1060 (1966).

<sup>24</sup> R. A. Benkeser, E. M. Kaiser, and R. F. Lambert, *J. Am. Chem. Soc.* **86**, 5272 (1964); *J. Org. Chem.* **34**, 3970 (1969).

<sup>25</sup> T. Osa, T. Yamagishi, T. Kodama, and A. Misono, *Symp. Synthetic Mechanistic Aspects Electroorg. Chem. Durham, North Carolina, 1968, Preprints of Papers* p. 157.

<sup>26</sup> H. W. Sternberg, R. E. Markby, J. Wender, and D. M. Mohilner, *J. Am. Chem. Soc.* **89**, 186 (1967); **91**, 4191 (1969).

<sup>27</sup> E. J. Hart, S. Gordon, and E. M. Frielden, *J. Phys. Chem.* **70**, 150 (1966).

<sup>28</sup> X. de Hemptinne and K. Schunk, *Ann. Soc. Sci. Bruxelles, Ser. I* **80**, 289 (1966); *Chem. Abstr.* **66**, 91139 (1967); *Trans. Faraday Soc.* **65**, 591 (1969).

the other to isopropanol. The rate of formation of these two products depends on the voltage and the history of the electrode.

Two types of adsorption of hydrogen are found—one of them being interstitial. The "interstitial" hydrogen is important in the electrocatalytic reduction of acetone to isopropanol, but not in the reaction leading to propane. At an anodically treated electrode no interstitial hydrogen is found, but its concentration gradually builds up. Besides being of importance in the reduction of substrate the interstitial hydrogen modifies the adsorption properties of the electrode, and the importance of the adsorption of the substrate at the electrode prior to the reduction is revealed by the kinetics of the reaction.

The reaction is dependent on time. At a freshly anodized electrode acetone is preferentially reduced to propane, whereas later isopropanol is the main product. Eventually both electrocatalytic reactions are suppressed and hydrogen evolution becomes the main reaction.

In many cases the formation of amalgams, active metals, hydrogen peroxide, halogens, or hydroxyl radicals has been postulated as the electrochemical step which then is followed by a purely chemical reaction. One of the usual arguments for these intermediates is that the reaction follows a route which may be duplicated by the chemical reagent, but this does not prove the presence of these intermediates in the electrolytic reaction.

The use of reversible redox systems in indirect electrolytic reactions may be of significance, especially in biological systems. Many of these systems comprise large molecules which diffuse slowly to the electrode and may lose some of their structural features on contact with the electrode, thereby becoming biologically inactive. In a number of cases this difficulty may be circumvented by using a suitable mediator to transfer the electrons between the biological redox system and the electrode.

### C. FACTORS INFLUENCING THE ELECTROLYTIC REACTION

Although the electrolytic reaction results in a reduction at a certain site in the molecule, it is the properties of the whole molecule which determine the energy, and thus the reduction potential, necessary for the transfer of the electrons to a suitable empty orbital. The presence of certain groups, however, makes the molecule reducible in most cases, and the rest of the molecule influences the reduction potential only to a minor degree. Such groups are often unsaturated,

such as the nitro, nitroso, carbonyl, and azomethine groups, but reductive cleavage of single bonds may also occur. The presence of electron-withdrawing groups facilitates the reduction, and the dependence of the reduction potential on the nature of the substituents in a series of compounds can often be represented by a Taft-Hammett type of equation.<sup>29</sup>

An electrolytic oxidation consists in a transfer of electrons from the molecule to the anode, and in a given series of compounds electron-donating groups, such as methoxy or amino groups, facilitate such a reaction.

The electrode potential determines which electrode reaction may occur; an electrolytic reaction can be controlled by means of the potential until and including the potential-determining step. The potential also governs the relative rate of an electron transfer and a competing chemical reaction thus affecting the product distribution in a branched reaction. Other factors, such as orientation of molecules at the electrode,<sup>30</sup> may be potential-dependent.

### 1. *Hydrogen Ions*

Hydrogen ions are involved in most electrode reactions involving organic compounds, and pH, therefore, affects the reduction potential. In addition, a change in pH may change the course of the electrode reaction; the reduction may take place in different parts of the molecule in acid and alkaline solutions, the number of electrons in the electrode reaction may depend on pH, or the stereochemistry of the product may be pH-dependent. In these cases the protonated form of the molecule is reduced differently from the unprotonated form, the former species being more easily reducible than the latter. Sufficient buffer capacity is necessary to ensure that the consumption of hydrogen ions in the electrode reaction does not change the pH in the immediate vicinity of the electrode. It thus produces complications in the study of electrode reactions to choose conditions for macroscale electrolysis near a pH at which a change in the electrode reaction takes place.

The choice of proton donors requires special consideration in aprotic media, as the use of too strong proton donors may lead to a preferential reduction of protons. The scarcity of protons in aprotic solvents is

<sup>29</sup> P. Zuman, "Substituent Effects in Organic Polarography." Plenum Press, New York, 1967.

<sup>30</sup> J. Volke and A. M. Kardos, *Collection Czech. Chem. Commun.* **33**, 2560 (1968).



valuable in the study of some electrode reactions, as intermediates, e.g., radical ions which in aqueous solution would react rapidly with protons or water may be sufficiently long-lived to be detected by ESR or trapped by reaction with a suitable reagent.<sup>31-34</sup>

## 2. Supporting Electrolyte

The accessible potential region at a certain electrode is dependent on the choice of *supporting electrolyte*. The alkali metal cations are reduced at about  $-2.0$  volts (SCE), whereas tetraalkylammonium ions can be used until about  $-2.5$  volts (SCE). These ions also interact with anion radicals to a lesser extent than the smaller alkali metal cations. This is of importance when using electrolytic reactions for the production of radicals for ESR measurements.<sup>35</sup> The tetraalkylammonium ions, however, are more strongly adsorbed at the electrode than the metal ions, and this may influence the kinetics of the reaction.

The choice of the anion is most important in anodic reactions. Perchlorates have been found very useful as they are difficult to oxidize and are often soluble both in water and nonaqueous solvents. In anodic (Section VI, F) or cathodic (Section IV, A) substitution reactions the nucleophilicity of the anion is of interest. High concentrations of tetraalkylammonium *p*-toluenesulfonates in water make the solubility of organic compounds higher than in pure water, and such solutions combine a low ohmic resistance with good dissolving power.

## 3. Electrode Material

The electrode material is important for several reasons. The magnitude of the hydrogen and oxygen overvoltage determines the accessible potential range; special surface properties, such as adsorptive and catalytic effects, may determine the course of the reduction. In the "electrocatalytic" reactions the electrochemical step consists in a reduction of hydrogen ions to adsorbed hydrogen, which then reacts with the substrate as in a catalytic reaction. The study of the influence of the electrode material on the course of the reaction is an area in which further research is very much needed.

<sup>31</sup> D. H. Geske and A. H. Maki, *J. Am. Chem. Soc.* **82**, 2671 (1960).

<sup>32</sup> B. L. Barton and G. K. Fraenkel, *J. Chem. Phys.* **41**, 1455 (1964).

<sup>33</sup> D. H. Geske and G. R. Padmanabhan, *J. Am. Chem. Soc.* **87**, 1651 (1965).

<sup>34</sup> J. C. M. Henning, *J. Chem. Phys.* **44**, 2139 (1966).

<sup>35</sup> T. Kitagawa, T. Layloff, and R. N. Adams, *Anal. Chem.* **36**, 925 (1964).

#### 4. Solvent

The solvent may influence the electrolytic reaction in different respects. The solubility of the substrate in the solvent is important for the attainment of a high initial current; the solubility of a supporting electrolyte and the dielectric constant of the medium are reflected in the ohmic resistance. The adsorption of substrate on the electrode depends on the medium, and so does the availability of protons. Some solvents are, themselves, oxidized or reduced too easily to be useful. A review on the solvents of interest for electrolysis has recently been published;<sup>38</sup> it includes information on the solubility of supporting electrolytes, useful reference electrodes, and attainable potential range.

In some cases the solvent plays an active part in the chemical follow-up reactions occurring after the electrochemical step; an example is electrolytic methoxylation (Section V, A).

### D. DETERMINATION OF OPTIMUM CONDITIONS FOR ELECTROSYNTHESIS

Many variables are of importance in determining the course of an electrode reaction. In order to determine the optimum conditions for an electrosynthesis the use of current-voltage curves obtained at microelectrodes is of great value. A series of such curves are produced using different electrode materials, solvents, and pH; when mercury is used as the electrode material, the ordinary polarographic technique<sup>8-10</sup> is applied. With some experience it is possible from such a series of experiments to choose conditions suitable for the reaction.

The results from polarographic investigation may be found in the literature, where a reproduction of the experimental curves (e.g., Fig. 10, p. 308), a graphical plot of the half-wave potentials and the limiting currents as a function of pH (e.g., Figs. 2 and 3), or a table gives the required data. Reviews of polarographic papers appear every second year.<sup>37-39</sup>

<sup>38</sup> C. K. Mann, in "Electroanalytical Chemistry" (A. J. Bard, ed.), Vol. 3, Dekker, New York, 1969.

<sup>37</sup> S. Wawzonek, *Anal. Chem.* **28**, 638 (1956), **30**, 661 (1958), **32**, 144 R (1960), **34**, 182 R (1962).

<sup>38</sup> S. Wawzonek and D. J. Pietrzyk, *Anal. Chem.* **36**, 220 R (1964).

<sup>39</sup> D. J. Pietrzyk, *Anal. Chem.* **38**, 278 R (1966), **40**, 194 R (1968).

The polarographic data may be used as a guide for electrolysis, as illustrated by the following example. The half-wave potentials and limiting currents at different pH of 2,3-dihydro-2,3-dimethyl-1,4-phthalazinedione (1)<sup>40</sup> are plotted in Fig. 2. In acid solution up to about pH 6 the half-wave potentials vary linearly with pH; about pH 7 the first wave disappears and another one appears at a more

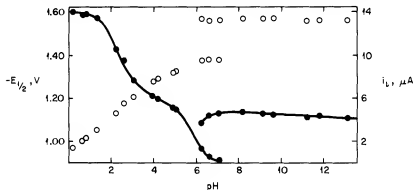


FIG. 2. Dependence on pH of the limiting current ( $\mu\text{A}$ ),  $\bullet\bullet\bullet$ , and the half-wave potentials (SCE),  $\circ\circ\circ$ , of 2,3-dihydro-2,3-dimethyl-1,4-phthalazinedione (1). Concentration  $2.0 \times 10^{-4} M$ . From Lund.<sup>40</sup>

negative potential which does not vary with pH. This indicates that the species reduced in acid solution has one more proton than that reduced in alkaline, and in this case the monoprotonated compound is reduced at low pH. The limiting current in strongly acid solution is approximately three times as high as that in alkaline medium for the same concentration which means that three times as many electrons are involved in the electrode reaction responsible for the first wave at pH 0 as for the second wave. Between pH 1 and 5 the height of the first wave diminishes gradually and reaches the height of a two-electron reduction at pH 5.

The electrode reactions were investigated by reducing the compound at pH 0 and 9; the reduction in acid solution produced 2-methyl-phthalimidine (2) by a six-electron reaction, whereas that at pH 9 yielded 3,4-dihydro-2,3-dimethyl-4-hydroxy-1-phthalazinone (3) in a two-electron reduction. This compound (3) was then investigated polarographically (Fig. 3); it is reduced in acid solution in 2 two-electron waves, at pH 4 in 2 one-electron waves, and not reducible in

<sup>40</sup> H. Lund, *Collection Czech. Chem. Commun.* **30**, 4237 (1965).

alkaline solution. It is of interest that the compound is, when reducible, more easily reduced than the starting material.

Compound **3** was then reduced in hydrochloric acid at the potential of the first wave (0.7 volt vs. SCE); the product obtained is 3,4-dihydro-2,3-dimethyl-1-phthalazinone (**4**), this product is also obtained from **1** in a four-electron reaction at pH 5.

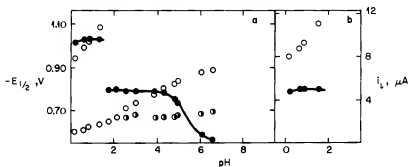


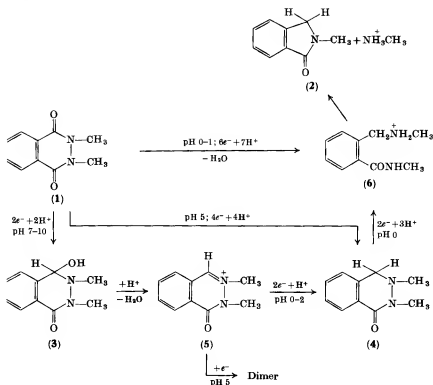
FIG. 3. Dependence on pH of the limiting current ( $\mu A$ ), ●●●, and the half-wave potentials (SCE) ○○○. (a) 3,4-Dihydro-2,3-dimethyl-4-hydroxy-1-phthalazinone (**3**) and (b) 3,4-dihydro-2,3-dimethyl-1-phthalazinone (**4**). Concentration  $2.0 \times 10^{-4} M$ . From Lund.<sup>40</sup>

The fact that the polarographic data for **1** at pH 5 suggests a two-electron reaction, whereas the preparative results prove a four-electron reduction, means that a slow chemical step occurs after the uptake of two electrons. The partly reduced molecule diffuses from the microelectrode before the chemical follow-up reaction has occurred, but this does not matter in an exhaustive, preparative reaction. The rate of the slow step is pH-dependent and this step is not apparent at low pH where it is sufficiently fast. The slow step is suggested to be the acid-catalyzed dehydration of **2** to the quaternary phthalazinone (**5**).

Finally, **4** was polarographed (Fig. 3); the wave of **4** appears at the same potential as that of the second wave of **3**. Reduction of **4** yields a mixture of 2-methylphthalimidine and its precursor, *N*-methyl-2-(methylaminomethyl)benzamide (**6**).

The results are presented in Scheme 1, and it is postulated that the reduction of **1** to 2-methylphthalimidine (**2**) proceeds through **3**, **5**, **4**, and **6**.

The information thus obtained is very valuable for the choice of experimental conditions; it must, however, be kept in mind that

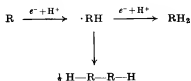


SCHEME 1

there are cases where differences between the results obtained in micro- and macroelectrolysis occur.<sup>41</sup> This is primarily caused by differences between micro- and macroscale experiments with respect to the concentrations ordinarily employed and to the duration of the experiments.

Sometimes the height of the polarographic wave points to an uptake of, e.g., two electrons, whereas a preparative reduction proceeds with  $n < 2$ . This difference can be caused by two types of mechanism. One of these types operates when the reduction proceeds through a radical which either can be reduced further or can dimerize according to Scheme 2.

<sup>41</sup> H. Lund, *Lecture, 19th Intern. Congr. Pure Appl. Chem., London, 1963, Abstr. p. 466.*



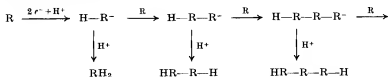
SCHEME 2

The dimerization often, but not always, takes place at the surface of the electrode, where the radicals are stabilized by partly bonding to the electrode. With increasing concentration of the radicals, the rate of the dimerization (second-order reaction) increases faster than the further reduction, and the electron consumption decreases. This mode of reaction often operates when the radical formed is fairly stable.

Sometimes the radicals, perhaps in some cases in the form of organic mercury compounds, form a layer on the electrode which makes the surface less accessible for the unreduced molecules, so they require a slightly more negative potential for the reduction. This phenomenon is less noticeable at the low concentrations normally employed in polarography where a low degree of coverage of the electrode is found and where a fresh surface is produced at the growing mercury drop.

In such cases the dimerized compound can be prepared by employing a high concentration of the reducible compound and stirring the mercury electrode, so that a fresh surface is produced, while the electrode potential is kept at a value corresponding to the foot of the polarographic wave. If the further reduced compound is the desired product, only the solution is stirred, and the potential is kept at a potential on the diffusion plateau of the wave.

If the radical formed is not stable or stabilized at the electrode, it is instantly reduced further. The carbanion thus produced may either react with hydrogen ions or with the reducible, unsaturated material according to Scheme 3.



SCHEME 3

Besides the simple reduction, a di-, tri-, or polymerization may thus result, depending, *inter alia*, on the concentration of the compound and the availability of protons. The overall electron consumption decreases in comparison with that indicated by the polarographic wave.

The differences in concentration between the micro- and macroscale experiments also affect the separation of the waves. The waves of irreversibly reduced compounds cover a greater potential range at higher concentrations than at lower concentrations. A reduction which in the microscale experiments gives two separate reduction waves may be difficult to carry out as a selective reaction. The best way to get a partial reduction in such a case is to use a potential at the foot of the composite wave.

Differences between the micro- and macroscale experiments may also be caused by differences in their duration. If a slow step occurs in the reaction after the uptake of some electrons, the reduced compound may diffuse away from the electrode before it is reduced further. At the microelectrode the concentration of the partly reduced species remains low and does not influence the polarographic curve visibly; in an exhaustive macroscale electrolysis a higher concentration of the partly reduced species is built up and the compound may or may not be reduced further when it diffuses to the electrode, depending on its reduction potential. If the reduction potential of the partly reduced species is more negative than that of the starting material, the partly reduced species can be obtained in a macroscale reduction at a suitable potential, and the difference between the micro- and macroscale experiments is that further reduction is not visible on the polarograms, although the macroreduction shows that a reducible compound is formed.

Sometimes more waves are visible on the polarograms than can be realized by macroelectrolysis. Some may be catalytic waves, and sometimes it is found that the product from the first reduction does not give these waves. In these cases a tautomeric change similar to that described later in the reduction of some cyclic azines may be operating so that it is the primarily formed species which is responsible for the observed waves, whereas the more stable tautomeric form is reduced by another route.

When the partly reduced species is more easily reduced than the starting material, a macroelectrolysis will show a higher electron consumption than that corresponding to the height of the polarographic wave. During a macroscale electrolysis the partly reduced

species may be detectable polarographically in the reaction mixture; it may produce a small wave at a less negative potential than that of the starting material. The concentration of the intermediate will remain low as it is reduced in preference to the starting material. Only if it is possible to trap the intermediate as a nonreducible derivative, can it be obtained as a product from the reduction.

As the polarographic curve, furthermore, can be influenced by certain compounds or inhibitors, adsorption phenomena can complicate the interpretation of the curves, and "catalytic" waves may suggest further reductions than those found by macroelectrolysis, a certain caution must be exercised in evaluating the voltammetric data. In most cases, however, no complications arise, and with a little experience the differences mentioned above are not serious drawbacks, but are of value as the combination of polarography and macroelectrolysis then throws light on one or more of the steps in the reaction.

Sometimes a product obtained by prolonged electrolysis with the dropping mercury electrode differs from that isolated from a macro-scale electrolysis at a mercury-pool electrode; the reason for this difference is not well understood. Such an example is described later (Section VI, G).

### E. CONTROL OF THE ELECTROLYTIC REACTION

In the classical electrolytic experiments the current density, measured in A/dm<sup>2</sup>, was the quantity which was controlled, possibly because it was the easiest factor to measure and keep constant. For a long time nearly all electrolytic reactions were performed with a control of the current density, although Haber,<sup>42, 43</sup> as early as 1898 in his famous papers on the stepwise reduction of nitro compounds, realized that the potential of the working electrode was the proper quantity to control.

The difference between the two ways of controlling the electrolytic reaction is illustrated in Fig. 4, which shows polarograms of the catholyte recorded during the controlled potential reduction (at -0.65 volt vs. SCE) in hydrochloric acid of 4-hydroxycinnoline (7) to 1,2,3,4-tetrahydro-4-cinnolone (8).<sup>44</sup>

<sup>42</sup> F. Haber, *Z. Elektrochem.* **4**, 506 (1898).

<sup>43</sup> F. Haber, *Z. Physik. Chem.* **32**, 193 (1900).

<sup>44</sup> H. Lund, *Acta Chem. Scand.* **21**, 2525 (1967).



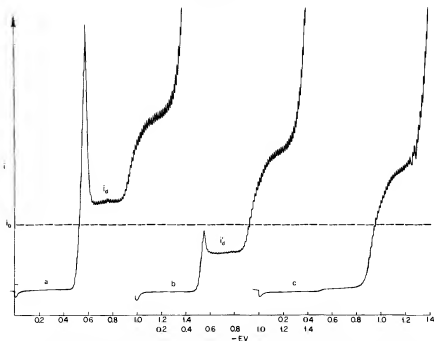
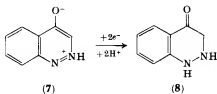


FIG. 4. Polarograms obtained during a controlled potential ( $-0.65$  volt vs. SCE) reduction of 4-hydroxyeinnoline. (a) Initial solution, (b) partly reduced solution, and (c) nearly completely reduced solution (see text).



Curve a indicates the dependence of the current on the cathode potential of the unreduced solution; below  $-0.45$  volt (SCE) no electrons are transferred, but between  $-0.45$  and  $0.60$  volt the electrons gradually get enough energy to be transferred to the substrate. The polarographic curve is in this case distorted by a so-called maximum which may be of first or second order. Between  $-0.6$  and  $-0.85$  volt the current is determined by the rate of transportation of substrate to the electrode surface, as the potential has a value where all molecules of 7 are reduced very quickly to 8, when they reach the

electrode. This diffusion current  $I_d$  is proportional to the concentration of **7** and to the number of electrons transferred in the electrode reaction.

Between  $-0.85$  and  $-1.0$  volt (SCE) the second electrode reaction, the reduction of the carbonyl group of **8** to alcohol or pinacol, begins, and at  $E < -1.2$  volts the reduction of hydrogen ions competes with the other reactions.

When the reduction is performed at  $-0.65$  volt (SCE), the potential never reaches a value where the second electrode reaction can take place; the reduction is selective. Curves b and c are polarograms taken when about half of and most of **7** is reduced to **8**. The height of the first wave, which is a measure of the concentration of **7**, decreases, whereas that of the second wave does not. In the present case the height of the second wave actually increases somewhat, which may be connected with adsorption phenomena or the change in medium as a result of the reduction of **7** to **8**.

If the current is held constant at  $I_0 < I_d$  (Fig. 4), the potential acquires a value of about  $-0.6$  volt, and the reaction is selective under such conditions. If the concentration of the reducible compound is kept at such a value that the limiting current is higher than the applied current, the reaction will remain selective. Such a situation requires a continuous addition of substrate and removal of products, and this approach is the most practical one for an industrial application of controlled potential reactions.

The "classical" constant current density experiments were not run as continuous processes, and the concentration of the reducible material diminished gradually. When the limiting current  $I_d$  becomes smaller ( $I_d'$ ) than the applied current  $I_0$ , the potential is forced to a more negative value, when the next electrode reaction takes place. Figure 4b illustrates this:  $I_0 > I_d'$  and the potential drops to about  $-0.94$  volt where the reduction of **8** also is possible. The two processes thus compete for the electrons and the reduction of **7** is no longer selective. Evidently one of the most advantageous features of the electrolytic process disappears when the classical constant current density technique is used.

### III. Apparatus

Only an introductory discussion of the practical problem will be presented, but supplementary information can be found in the references.

## A. ELECTRODES

A common controlled potential electrolysis requires three electrodes—a cathode, an anode, and a reference electrode, of which either the cathode or the anode is the working electrode.

As reference electrode any electrode whose potential is well defined and constant may be used; by far the most widely used reference electrodes in aqueous and partly aqueous solution are the calomel (SCE, saturated calomel electrode) and the silver/silver chloride electrodes, both of which are electrodes of second kind. In non-aqueous solutions quite a few other reference electrodes have been used besides the calomel electrode. A discussion of reference electrodes is included in standard monographs on electroanalytical techniques, and comparisons between the different types of electrode have been made.<sup>45-48</sup>

The material making up the working electrode is important to the course of the electrode reaction. The choice of anode material is rather limited as many materials are oxidized too easily to permit the use of the required potentials. Platinum, platinized titanium, gold, carbon, lead, and lead-silver alloys are the most common anodic materials. For cathodes the choice is much wider; here properties such as hydrogen overvoltage, catalytic effect, and reproducibility of the surface, play an important role. Mercury has been much used in laboratory work as it has a high hydrogen overvoltage, a low catalytic effect, and a reproducible, clean surface; it has also been of importance in that the use of the dropping mercury electrode is a standard analytical procedure. Discussions of electrode materials are found in different monographs. Much research is needed to throw light on the influence of electrode material on the course of the electrode reactions.

The design of the electrodes may be of importance; by special machining of the electrode surface it has been possible to obtain a "wicking" effect so a higher current density than usual can be applied.<sup>49</sup>

<sup>45</sup> J. P. Billon, *J. Electroanal. Chem.* **1**, 486 (1960).

<sup>46</sup> R. C. Larson, R. T. Iwamoto, and R. N. Adams, *Anal. Chim. Acta* **25**, 371 (1961).

<sup>47</sup> G. Le Guillanton, *Bull. Soc. Chim. France* 2359 (1963).

<sup>48</sup> K. Tsuji and P. J. Elving, *Anal. Chem.* **41**, 216 (1969).

<sup>49</sup> G. T. Miller, *Electrochem. Soc. Sect. Meeting, Detroit, 1968*.

## B. CELLS AND CIRCUITS

The design of an electrolytic cell for a controlled potential reaction may vary widely<sup>2, 50-53</sup>; in the construction of such cells, problems such as ohmic resistance, cooling, flexibility, durability, choice of diaphragm to separate anode and cathode compartments, and ease of construction are considered.

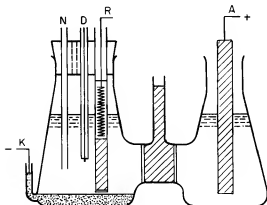


Fig. 5. Cell for preparative reduction (K, mercury cathode; A, carbon anode; R, reference electrode; D, dropping mercury electrode; N, inlet for nitrogen). From Lund.<sup>54</sup>

For batch electrolysis on a laboratory scale (100 mg to 100 gm) the author has for many years used the two types shown in Figs. 5<sup>54</sup> and 6.<sup>55</sup> The first one (Fig. 5) is a divided, slightly modified Lingane cell made from two 250-ml conical flasks; in this cell batches from 0.1–5

<sup>50</sup> K. Sugino, K. Shirai, T. Sekine, and K. Odo, *J. Electrochem. Soc.* **104**, 867 (1957).

<sup>51</sup> O. Manousek and P. Zuman, *Collection Czech. Chem. Commun.* **29**, 1718 (1964).

<sup>52</sup> R. Kanakam, M. S. V. Pathy, H. V. K. Udupa, *Electrochim. Acta* **12**, 329 (1967).

<sup>53</sup> A. P. Tomilov and V. A. Klimou, *Elektrokhimiya* **3**, 232 (1967); **2**, 1405 (1966).

<sup>54</sup> H. Lund, "Elektrodereaktioner i organisk polarografi og voltammetri." Aarhus Stiftsbogtrykkerie, Aarhus, 1961.

<sup>55</sup> P. E. Iversen and H. Lund, *Acta Chem. Scand.* **19**, 2303 (1965).

gm are conveniently handled. The second cell (Fig. 6) is made from a 2-liter beaker. It has the anode compartment in the center of the cell; the anode chamber is quite small and therefore it is necessary to circulate the anolyte continuously. This cell has been used for larger preparations (30–100 gm) using currents up to 25 Amp. For the reduction of larger amounts of material it may be practicable to circulate both the catholyte and the anolyte.

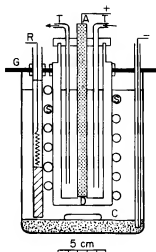


FIG. 6. Cell for macroscale electrolysis at controlled potential consisting of a 2-liter beaker covered with a glass plate G, containing holes for a silver/silver chloride reference electrode R, the anode compartment, a cooling coil S, a thermometer, an inlet for nitrogen, and one for withdrawing of samples. The mercury cathode C has an area of 125 cm<sup>2</sup>. The diaphragm D consists of two porous clay cylinders separated by agar containing KCl. The anolyte (15% aqueous NaOH) is continuously renewed through T. Anode A is of stainless steel. From Iversen and Lund.<sup>55</sup>

The higher the applied current is, the more critical becomes the design of the cell; the ohmic resistance must be kept low, and it is especially important that the tip of the reference electrode (the "Luggins capillary") ends close to the working electrode. Otherwise, the inevitable potential drop due to the ohmic resistance between the working electrode and the "Luggins capillary" (the "*IR*-drop") becomes intolerably great.<sup>56, 57</sup>

For cells with continuous addition of reducible material and removal of product, the design depends on the techniques for the addition and removal. A cell designed for the hydrodimerization of acrylonitrile to adiponitrile is shown in Fig. 7.<sup>58</sup>

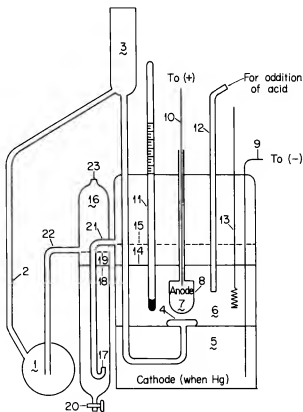


FIG. 7. Schematic drawing of continuous laboratory cell. 1, Boiler; 2, riser; 3, condenser; 4, disperser; 5, cathode when Hg; 6, catholyte solution; 7, anode chamber; 8, diaphragm; 9, lead to cathode; 10, lead to anode; 11, thermometer; 12, inlet tube; 13, stirrer; 14, catholyte level; 15, level of supernatant AN; 16, washer; 17, disperser; 18, water level; 19, supernatant level; 20, stopcock; 21, overflow tube; 22, overflow tube; and 23, water inlet. From Baizer.<sup>58</sup>

<sup>56</sup> D. Peltier and C. Moinet, *Bull. Soc. Chim. France* 2657 (1968).

<sup>57</sup> C. Moinet and D. Peltier, *Bull. Soc. Chim. France* 690 (1969).

<sup>58</sup> M. M. Baizer, *J. Electrochem. Soc.* **111**, 215 (1964).

A circuit for manual control of the working potential is shown in Fig. 8<sup>54</sup>; it is made from components available in all laboratories. It includes, besides the cell, a high-resistance voltmeter or pH-meter, an ammeter, a coulometer, and a dc source. With the voltage adjuster the voltage across the cell is set to such a value that the potential difference between the working and the reference electrodes has the desired value; the voltage between the anode and cathode is, as such, not important because it includes the potential drop caused by the ohmic resistance.

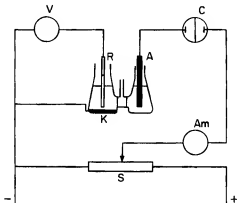


FIG. 8. Circuit for constant potential reduction. K, Cathode; A, anode; R, reference electrode; V, potentiometer or pH-meter; C, coulometer; Am, ammeter; and S, voltage adjuster. From Lund.<sup>54</sup>

The manual control can be replaced by electronic control using a potentiostat. Such apparatus is commercially available from several companies of which each has a number of different models, often at a reasonable price. Potentiostats may also be built according to published diagrams.<sup>59, 60</sup>

#### IV. Electrolytic Formulation of Heterocyclic Systems

In Section IV we will discuss the electrolytic reactions in which a heterocyclic system is formed; the reactions will be treated under the

<sup>59</sup> J. J. Lingane, "Electroanalytical Chemistry," 2nd ed., p. 296. Interscience, New York, 1958.

<sup>60</sup> G. L. Booman and W. B. Holbrook, *Anal. Chem.* **35**, 1793 (1963).

following headings: ring closure reactions, ring contractions, and ring expansions.

### A. RING CLOSURE REACTIONS

In the electrolytic formation of heterocyclic systems the role of the current is to bring one or both of the reaction centers to a suitable oxidation state. These reactions may be classified in different ways; here they are treated according to the type of bond formed.

#### 1. Formation of Carbon-Nitrogen Bonds

A ring closure of this type will most often involve either the attack of an electrolytically formed nucleophile (hydroxylamine, amine, or hydrazine) on an electrophilic center (existing or potential carbonyl, cyano, nitro, or nitroso group) or a reaction between a nucleophile and an electrolytically generated electrophilic center (e.g., nitroso group or carbonium ion).

a. *Hydroxylamino Group as Nucleophile.* Aromatic nitro compounds may generally be reduced in a four-electron reduction to hydroxylamines which in acid solution at a more negative potential can be reduced further to amines. By choosing a suitable cathode potential it is thus possible to avoid the further reduction. When a hydroxyl or amino group is ortho or para to the nitro group, it is not possible to isolate the hydroxylamino compound, as it is too easily dehydrated to the reducible quinone mono- or diimine; it may, however, be possible to trap the intermediate.

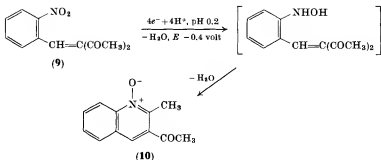
i. *Reaction with carbonyl groups.* A hydroxylamino group has two nucleophilic centers, the nitrogen and the oxygen atom. Whenever attack of the nitrogen atom on a carbonyl group would result in the formation of a ring having five or more members, this mode is preferred to attack by oxygen. The reaction results in a cyclic nitrone (*N*-oxide) or hydroxamic acid.

The reduction of *o*-nitrobenzalacetylacetone (9) in acid solution at the potential of the first polarographic wave gives the cyclic *N*-oxide (10).<sup>61, 62</sup> The isolated yield is 70–75%, but a polarographic determination of the product in the reduced solution showed a somewhat

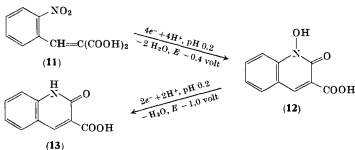
<sup>61</sup> H. Lund, *Symp. Synthetic Mechanistic Aspects Electro-org. Chem., Durham, North Carolina, 1968, Preprints of Papers p. 197.*

<sup>62</sup> H. Lund and L. G. Feoktistov, *Acta Chem. Scand.* **23**, 3482 (1969).

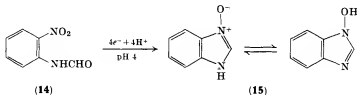




higher yield. Compound (10) may at a more negative potential be reduced further, but the reduction potentials of the *N*-oxide and the carbonyl group are rather close in acid solution, making selective reduction of the *N*-oxide difficult.



*o*-Nitrobenzalmalonic acid (11) can be reduced in a four-electron reduction,<sup>63</sup> and the resulting cyclic hydroxamic acid (12) is, like many other hydroxamic acids, further reducible in acid solution to the amide, the carbostyryl (13).



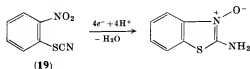
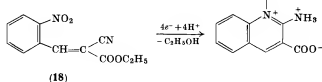
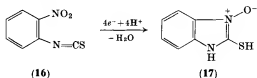
<sup>63</sup> H. Lund and J. Hakl, Unpublished observation.

Similarly, *o*-nitroformanilide (14) gives on reduction in acetate buffer benzimidazole *N*-oxide (1-hydroxybenzimidazole, 15), but the isolated yield in this case is rather low (20%).<sup>62</sup>

Although only a few examples have been reported so far, there seems no reason to doubt that good yields of similar products may be obtained in many cases.

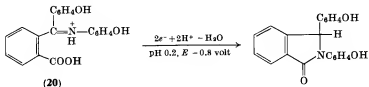
ii. *Reaction with potential carbonyl groups.* In principle, similar condensations to those described for carbonyl groups are possible for the corresponding azomethine compounds. An example of this kind is the reduction of 2-nitrophenylisothiocyanate (16) in ethanolic hydrochloric acid, which in a four-electron reduction forms 2-mercaptobenzimidazole *N*-oxide (17).<sup>62</sup>

iii. *Reaction with cyano groups.* These reactions are similar to those described above. The following examples, the reduction of *o*-nitrobenzalcyanoacetic ester (18)<sup>62</sup> and *o*-nitrophenylthiocyanate (19),<sup>62</sup> may illustrate this.



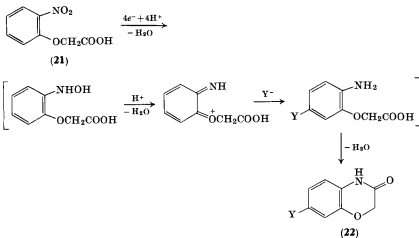
b. *Amines as Nucleophiles.* Amines may be formed by the electrolytic reduction of azomethine derivatives and nitro, nitroso, and hydroxylamino compounds. As the amine is the lowest oxidation state, control of the electrode potential is often not as critical in the preparation of amines as in the synthesis of hydroxylamines. Consequently, most of the "classical" electrolytic reductions of nitro compounds in acid solution resulted in the formation of amines.

i. *Reaction with carbonyl groups.* Cyclization of an azomethine compound occurs in the reduction of "phenolphthalein oxime" (20)<sup>64</sup> and similar very stable anils.<sup>65</sup>



The reduction of *o*-nitroacetanilide to 2-methylbenzimidazole<sup>66, 67</sup> and of 2-nitrophenylthiocyanate to 2-aminobenzothiazole<sup>68</sup> have been reported, but when no other reducible groups are present the advantage of using electrolytic methods for the reduction is questionable.

Sometimes a "cathodic substitution" reaction takes place during the reduction of ortho-substituted nitrobenzenes; thus the reduction of 2-nitrophenoxyacetic acid (21) in 2 *N* hydrochloric acid (50% ethanol) yielded 5-chloro-2*H*-1,4-benzoxazin-3(4*H*)-one (22),  $\text{Y} = \text{Cl}$ ) rather than the expected cyclic hydroxamic acids<sup>62</sup>; in the presence of another nucleophile  $\text{Y}^-$  (e.g., thiocyanate) ring substitution with this reagent occurs.



<sup>64</sup> H. Lund, *Acta Chem. Scand.* **14**, 359 (1960).

<sup>65</sup> H. Lund, P. Lunde, and F. Kaufmann, *Acta Chem. Scand.* **20**, 1631 (1966).

<sup>66</sup> K. Brand and E. Stohr, *Ber.* **39**, 4058 (1906).

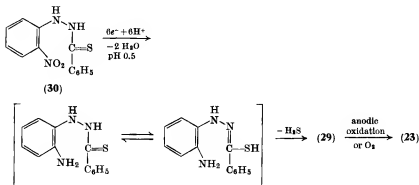
<sup>67</sup> M. Le Guyader, *Bull. Soc. Chim. France* 1867 (1966).

<sup>68</sup> F. Fichter and T. Beck, *Ber.* **44**, 3636 (1911).



buffer by a four-electron reduction into *o*-nitrophenylbenzhydrazidoxime (**25**), which at a more negative potential is reduced to *o*-nitrophenylbenzamidrazone (**26**) and then to *o*-aminophenylbenzamidrazone (**27**). Ring closure through **28** follows to give 1,4-dihydro-3-phenylbenzo-1,2,4-triazine (**29**) which is oxidized to **23**; a high yield (85–96%) of this compound may be obtained in hydrochloric acid solution or acetate buffer containing DMF by reduction at the potential of the second wave.

Other leaving groups may be used<sup>70</sup>; thus, thiobenz(*o*-nitrophenyl)-hydrazide (**30**) gives a good yield of **29** on reduction, but benz(*o*-nitrophenyl)hydrazide does not. This is probably because the hydroxyl group is a poorer leaving group than the amino or sulfhydryl group; the product analogous to **28** does not lose water, but opens to *o*-hydrazinobenzanilide which forms a benzimidazole on ring closure.

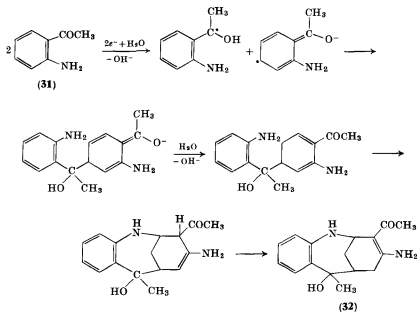


Attempts to reduce benzaldehyde-*o*-nitrophenylhydrazone to benzaldehyde-*o*-hydroxylaminophenylhydrazone which on ring closure might form the dihydrobenzotriazine were not successful,<sup>70</sup> as it was not possible to avoid the further reduction to amine. A similar situation is also found in the reduction of *o*-nitroanilines.

It is thus essential that the central carbon atom is in the oxidation state of a carboxyl group and carries a good leaving group. If the central carbon atom is in a lower oxidation state, it must be oxidized before reduction of the aromatic nitro group. Benzaldehyde-*o*-nitrophenylhydrazone may thus be nitrosated<sup>70</sup> and further oxidized to *o*-nitrophenylazophenylnitromethane which as described forms **29** in two steps with the consumption of altogether twelve electrons.

c. *Ring Closure by Michael Addition.* Electrolytic reduction of

*o*-aminoacetophenone (**31**) or 3-methylantranil in alkaline solution yielded<sup>71</sup> some of the expected alcohol (8%), the *d,l*-pinacol (21%), and *meso*-pinacol (9%). Two stereoisomers (23 and 35% yield) of 3-acetyl-4-amino-7-hydroxy-7-methyl-2,6-methano-2,5,6,7-tetrahydro-1(*H*)-benzazonine (**32**) were also formed. The reaction mechanism in Scheme 5 has been suggested.<sup>71</sup>

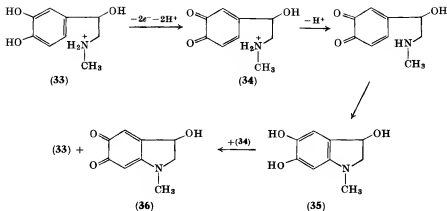


SCHEME 5

An oxidatively induced ring closure occurs during the oxidation of various catecholamines (**33**)<sup>72</sup> at a carbon paste electrode. Whereas the oxidation in 1 *M*  $\text{H}_2\text{SO}_4$  yielded the 1,2-benzoquinone (**34**), sufficient free amine of **34** was present at pH 3 to allow an internal Michael addition of the adrenaline quinone. As would be expected, the resulting catechol (**35**) is more easily oxidizable than adrenaline and is converted into the quinone adrenochrome (**36**) by chemical oxidation by adrenaline quinone.

<sup>71</sup> H. Lund and A. D. Thomsen, *Acta Chem. Scand.* **23**, 3567, 3582 (1969).

<sup>72</sup> M. D. Hawley, S. V. Tatawawadi, S. Piekarski, and R. N. Adams, *J. Am. Chem. Soc.* **89**, 447 (1967).



d. *Hydrazines as Nucleophilic Reagents.* Very few cases of hydrazines used as nucleophilic reagents have been reported. One of the reasons is that an azo compound having an amino or hydroxyl group para to the azo group is not reduced as a simple azo compound to the hydrazine but rather it is reduced as a quinone hydrazone to two amines in a four-electron reduction with cleavage of the nitrogen–nitrogen bond.

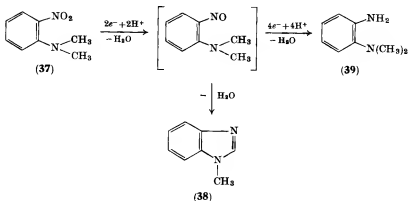
e. *Nitroso Groups as Electrophilic Centers.* Nitroso derivatives may be formed as intermediates in the reduction of nitro compounds, but as the nitroso group generally is more easily reducible than the nitro group, the lifetime of the nitroso stage is rather short. Alternatively, the nitroso compound may be prepared by anodic oxidation of a hydroxylamine at a platinum or carbon anode at a suitable pH.

Activated methyl groups may react with an intermediate nitroso group in acid solution; thus, o-nitrodimethylaniline (37) yields on reduction in 2 N HCl a mixture of N-methylbenzimidazole (38) and o-aminodimethylaniline (39).<sup>73</sup>

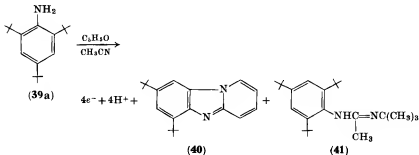
f. *Carbonium Ions as Electrophilic Centers.* Many aromatic compounds yield carbonium ions on oxidation at a platinum electrode in a nonaqueous solvent such as acetonitrile. 2,4,6-Tri-*t*-butylaniline (39a) yields 40 and 41 on anodic oxidation in acetonitrile containing pyridine.<sup>74</sup>

<sup>73</sup> M. Le Guyader and D. Peltier, *Bull. Soc. Chim. France* 2695 (1966).

<sup>74</sup> G. Cauquis, J.-L. Cros, and M. Genies, *Symp. Synthetic Mechanistic Aspects Electro-org. Chem., Durham, North Carolina 1968, Preprints of Papers* p. 249.



The reaction starts with loss of two electrons from the aromatic system of **39a**; this is stabilized by loss of a *t*-butyl carbonium ion, which reacts with acetonitrile in a Ritter-type reaction, and by attack by the nucleophile pyridine. The second loss of two electrons may occur before or after the ring closure. Similar internal substitution reactions are of potential value for the synthesis of heterocyclic compounds.



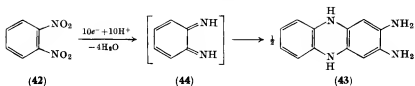
*g. Other Reactions.* In the reduction of *o*-dinitrobenzene (**42**) at pH 0 some 2,3-diamino-9,10-dihydrophenazine (**43**) is formed.<sup>75</sup>

The intermediate responsible for the ring closure is probably the *o*-quinone diimine (**44**).

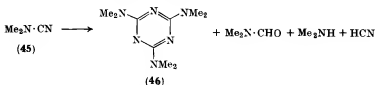
Electrolytic preparation of *sym*-triazines has been reported; electrolysis at a mercury cathode of *N,N*-dimethylcyanamide (**45**) containing lithium chloride as supporting electrolyte produced

<sup>75</sup> M. Breant and J.-C. Merlin, *Bull. Soc. Chim. France* 54 (1964).





2,4,6-tris(dimethylamino)triazine (46) together with some dimethylformamidine, dimethylamine, and HCN.<sup>76</sup> The effect of different substituents on the reaction has been investigated.<sup>77</sup> It was also found that a similar reaction mixture was obtained by treating 45



with lithium, but not with lithium amalgam. The formation of triazine is not a reduction, but the trimerization must be catalyzed by an electrolytically generated base.

## 2. Formation of Carbon-Oxygen Bonds

A ring closure of this type has been reported only in the reduction of *o*-nitrocarbonyl compounds to anthranils. Larger rings cannot be obtained by this method as attack by the nitrogen atom of the intermediate hydroxylamine would be the preferred mode.

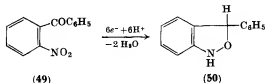
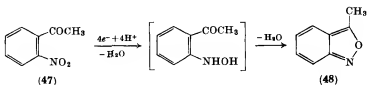
*o*-Nitroacetophenone (47) is reduced to methylanthranil (48) in sulfuric acid<sup>78</sup> and acetate buffer<sup>69</sup>; in the latter medium the yield is quantitative. *o*-Nitrobenzaldehyde<sup>78</sup> is reduced similarly and such a reduction might be expected in general from *o*-nitroaldehydes and *o*-nitroketones. The reduction of *o*-nitrobenzophenone (49)<sup>79</sup> has, however, been reported to yield the dihydroanthranil (50); this is surprising because a reduction of an intermediate anthranil would be expected to result in a hydrogenolysis of the nitrogen-oxygen bond rather than in a saturation of the double bonds.

<sup>76</sup> S. Takenaka and T. Sekine, *Denki Kagaku* **36**, 349 (1968); *Chem. Abstr.* **70**, 25097 (1969).

<sup>77</sup> S. Takenaka and T. Sekine, *Denki Kagaku* **36**, 863 (1968); *Chem. Abstr.* **70**, 92611 (1969).

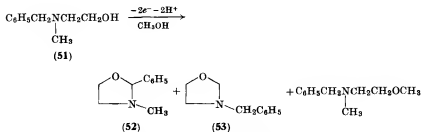
<sup>78</sup> M. Le Guyader, *Compt. Rend.* **C262**, 1383 (1966).

<sup>79</sup> C. Baezner and A. Gardiol, *Ber.* **39**, 2512 (1906).



3-Nitrophthalic acid<sup>80</sup> can be reduced in dilute sulfuric acid at a platinum cathode in high yield to 4-carboxy-benzisoxazolone. Benzisoxazolones are formed in the reduction of *o*-nitrobenzoic acid and its derivatives at a mercury cathode in acid solution at 60°C.

Anodic oxidation in alkaline methanol of *N*-benzyl-*N*-methylethanolamine (51) produces three main products<sup>81</sup>; two of these are 3-methyl-2-phenyloxazolidine (52) and 3-benzyl-oxazolidine (53). The primary loss of an electron occurs probably from the nitrogen



atom. *N*-Benzyl-diethanolamine produces similar products on anodic oxidation.<sup>81</sup>

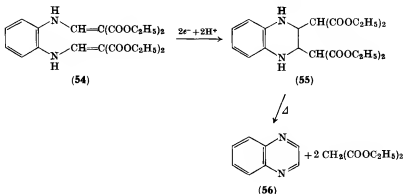
### 3. Formation of Carbon-Carbon Bonds

Electrolytic formation of carbon-carbon bonds occurs in the reduction of ketones to pinacols, in the Kolbe synthesis, and in the hydrodimerization of activated double bonds. Of these only the last reaction has been used in the preparation of heterocyclic compounds.

<sup>80</sup> K. Gleu and K. Pfannstiel, *J. Prakt. Chem.* [2] **146**, 129 (1936).

<sup>81</sup> N. L. Weinberg and E. A. Brown, *J. Org. Chem.* **31**, 4058 (1966).

*o*-Bis( $\beta$ -dicarbethoxyvinylamino)benzene (54) yields by intramolecular reductive coupling 2,3-bis(dicarbethoxymethyl)-1,2,3,4-tetrahydroquinoxaline (55), which on heating gives quinoxaline (56).<sup>82</sup>



#### 4. Formation of Nitrogen-Nitrogen Bonds

This type of ring closure is mostly achieved either by reaction between a hydroxylamino and a nitroso group or between a hydrazine derivative and a nitro or nitroso group.

A reductive coupling is possible whenever two aromatically bonded nitro groups are in such a position that a 6- or 7-membered ring may be formed. The coupling occurs probably between a hydroxylamino group and an intermediate nitroso group with the formation of a cyclic azoxy derivative, a heterocyclic *N*-oxide.

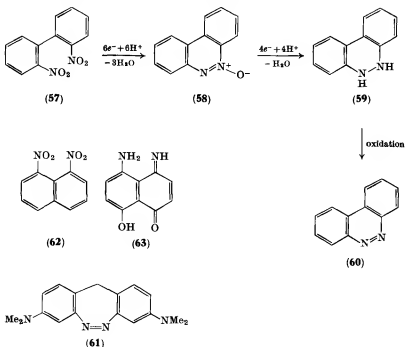
2,2'-Dinitrobiphenyl (57)<sup>44, 83</sup> is thus reducible in alkaline solution at a suitable potential to benzo[*c*]cinnoline *N*-oxide (58); in acid solution the reduction proceeds to 4,5-dihydrobenzo[*c*]cinnoline (59) which is very easily oxidized, e.g., by air, to benzo[*c*]cinnoline (60).

Similarly, 2,2'-dinitro-4,4'-bisdimethylaminodiphenylmethane is reduced to bisdimethylaminodibenzo[*c,f*]1,2-diazepine (61).<sup>69</sup> When a hydroxyl or amino group is para or ortho to the nitro groups, however, reduction to the amine without ring closure might be the observed reaction.

1,8-Dinitronaphthalene (62) could be expected to undergo ring closure on reduction, but suitable conditions have not yet been found;

<sup>82</sup> J. D. Anderson and M. M. Baizer, *Tetrahedron Letters*, 511 (1966).

<sup>83</sup> T. Wohlfahrt, *J. Prakt. Chem.* [2] **65**, 295 (1902).



the diamine<sup>84</sup> and 8-amino-5-hydroxy-1,4-naphthoquinone-1-imine (63)<sup>85</sup> have been reported as products.

When one of the nitro groups is aliphatically bonded, coupling may take place, although the yield is often somewhat lower. 2-Nitro-1-(2'-nitrophenyl)ethanol (64) can be reduced in acetate buffer in 2 four-electron steps. The dihydroxylamino (65) compound is transformed to cinnoline (66) by alkali. The reaction route of Scheme 6 has been suggested.<sup>86</sup>

Reduction of an azo compound to a hydrazine may lead to ring closure, when a nitro group is suitably situated. Thus the reduction of 4-hydroxy-2'-nitroazobenzene (67) in alkaline solution follows the upper scheme on p. 251.<sup>87, 88</sup>

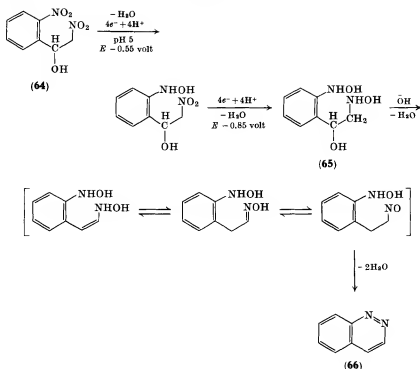
<sup>84</sup> J. Møller, *Elektrochem. Z.* **10**, 201 (1904).

<sup>85</sup> Bad. Anilin- und Sodafabrik, German Patent 79,406 (1894).

<sup>86</sup> H. Lund, *1st Intern. Congr. Heterocycl. Chem., Albuquerque, 1967*.

<sup>87</sup> K. Elbs and W. Keiper, *J. Prakt. Chem.*, [2] **67**, 580 (1903).

<sup>88</sup> H. Lund and S. Kwee, *Acta Chem. Scand.* **22**, 2879 (1968).



SCHEME 6

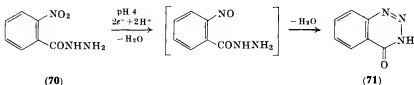
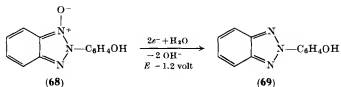
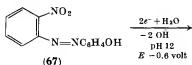
By controlling the electrode potential it is possible to prepare the *N*-oxide (68) in good yield,<sup>88</sup> whereas the "classical" procedure yields the benzotriazole (69).<sup>87</sup>

A hydrazide may also condense to some extent with an intermediate nitroso group,<sup>89</sup> but the yield obtained so far is low. *o*-Nitrobenzoic hydrazide (70) is reduced in acetic acid buffer to a mixture from which some benzo-1,2,3-triazinone-4 (71) has been isolated.

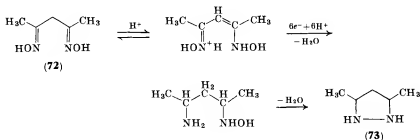
A reductive ring closure of a  $\beta$ -dioxime (72) to a pyrazolidine (73) was reported<sup>90</sup> to occur in 30% sulfuric acid at a lead cathode. The following mechanism (Scheme 7) may operate in which the loss of water from the intermediate hydroxylamine may be assisted by the acid.<sup>69</sup>

<sup>89</sup> L. G. Feoktistov and H. Lund, Unpublished observation.

<sup>90</sup> J. Tafel and E. Pfeffermann, *Ber.* **36**, 219 (1903).



The structure of the protonated oxime, which is substantiated by its NMR spectrum in trifluoroacetic acid,<sup>69</sup> may explain why the oxime is not reduced to the amine as other oximes.



SCHEME 7

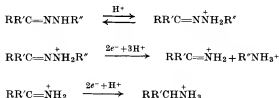
### B. RING CONTRACTIONS

In ring contractions occurring during electrolysis of nitrogen-containing heterocyclic compounds hydrogenolysis of a single bond takes place at some step, which is then followed by a ring reclosure. These reactions may be classified according to the single bond cleaved in the reduction; hydrogenolysis may take place at a nitrogen-nitrogen, nitrogen-oxygen, or nitrogen-carbon bond.

### 1. Hydrogenolysis of a Nitrogen-Nitrogen Bond

A ring contraction involving this reaction has been found in cyclic hydrazones, hydrazides, and triazenes.

The initial step in the reduction in acid solution of azines, hydrazones, and substituted hydrazones has been suggested to be a hydrogenolysis of the nitrogen-nitrogen bond.<sup>91</sup> The aldimine and ketimine thus formed are usually, but not always, reduced further at the potential necessary for the reductive cleavage; this depends on the nature of the substituents. The general reduction scheme for a hydrazone is shown in Scheme 8.



SCHEME 8

In the ring-closure step the amine  $\text{R}''\text{NH}_2$  attacks the imine with the formation of  $\text{RR}'\text{C}=\text{NR}''$  and loss of ammonia, and this reaction is to be expected whenever the imine is not reducible at the potential necessary for the reductive ring opening.

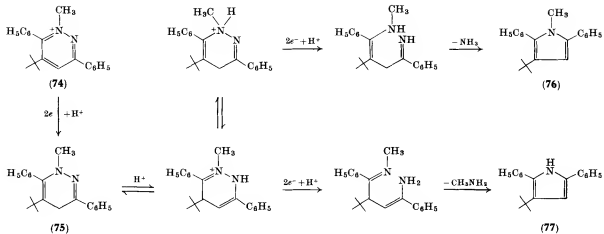
a. *Pyridazines to Pyrroles*. Pyridazines are generally reduced to dihydropyridazines which can exist in different tautomeric forms; the reduction pathways of these may be different. In the reduction in acid solution of 1-methyl-3,6-diphenyl-5-*t*-butylpyridazinium iodide (**74**) the following reaction sequence (Scheme 9) has been found.<sup>92</sup> The pyrroles (**76**) and (**77**) were formed from **75** in the ratio 3:1.

b. *Cinnolines to Indoles*. 1,4-Dihydrocinnolines (**78**), obtained by reduction of cinnolines (**79**) at a potential corresponding to the first polarographic wave, are further reducible in acid solution,<sup>44</sup> and thus resemble phenylhydrazones.

The reduction route through the imine (**80**) has been postulated because a polarographic wave which could be due to this compound is found when **78** is polarographed. 1,4-Dihydrocinnolines may rearrange

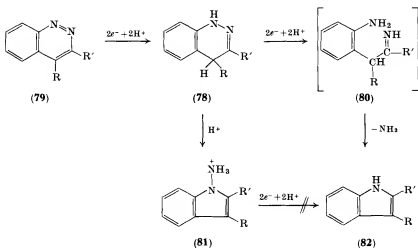
<sup>91</sup> H. Lund, *Acta Chem. Scand.* **13**, 249 (1959).

<sup>92</sup> H. Lund and P. Lunde, *Acta Chem. Scand.* **21**, 1067 (1967).



SCHEME 9

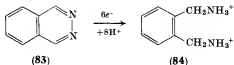




to *N*-aminoindoles (81) in strong acid, but this compound is not further reducible under the conditions employed and is therefore not an intermediate.

The reduction of dihydrocinnolines to indoles (82) may generally be expected, except when a substituent at C-3 renders the ketimine (80) reducible at the potential employed.

c. *Phthalazines to Isoindole Derivatives.* Whereas phthalazine (83) is reduced polarographically<sup>93</sup> by a six-electron reduction in strongly acid solution to *o*-xylene- $\alpha, \alpha'$ -diamine (84), 1-methylphthalazine (85) is reduced in two steps, a four-electron reduction followed by a two-electron reduction.<sup>94</sup> The following reaction scheme (85-87) with

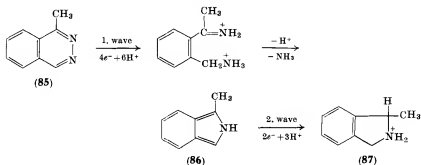


an intermediate formation of the reducible isoindole (86) has been suggested.<sup>94, 95</sup> 86 can be isolated as its hydrochloride.<sup>95</sup>

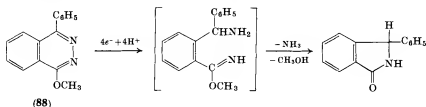
<sup>93</sup> C. Furlani, S. Bertola, and G. Morpurgo, *Ann. Chim. (Rome)* **50**, 858 (1960).

<sup>94</sup> H. Lund, *Discussions Faraday Soc.* **45**, 193 (1968).

<sup>95</sup> H. Lund and E. T. Jensen, *Acta Chem. Scand.* **24** (1970) in press.

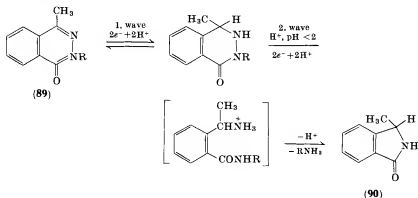


A similar reaction sequence is expected from some other phthalazine derivatives, such as methoxy (88) and aminophthalazines,<sup>95</sup> e.g., Scheme 10.



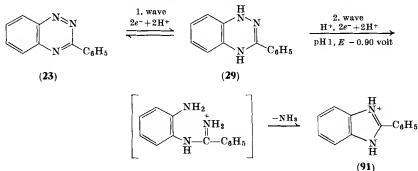
SCHEME 10

Phthalazinones are, so far, the only hydrazones in which, in acid solution, the carbon-nitrogen double bond has been shown to be saturated before the hydrogenolysis of the nitrogen-nitrogen bond.<sup>40</sup> 4-Methylphthalazinone (89) is thus reduced in the following steps to 1-methylphthalimidine (90).

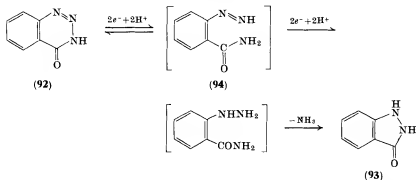


A similar ring contraction has been observed during the reduction in acid solution of 2,3-dimethyldihydrophthalazinedione.<sup>40</sup>

d. *Benzo-1,2,4-triazines to Benzimidazoles.* The reduction of 3-phenylbenzo-1,2,4-triazine (**23**)<sup>70,96</sup> to 2-phenylbenzimidazole (**91**) is of the same type as the reduction of dihydrocinnolines. The structure of the dihydrobenzotriazine has not been proved, but is probably that of the 1,4-dihydro derivative (**29**).



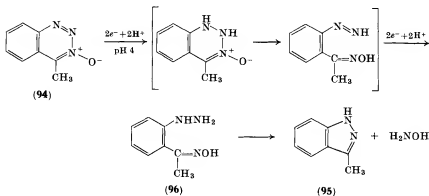
e. *Benzo-1,2,3-triazinone to Indazolone.* 3,4-Dihydro-4-oxobenzo-1,2,3-triazine (**92**) is reduced in both acid and alkaline solutions by a four-electron reaction<sup>97</sup> to indazolone (**93**). As a small polarographic prewave was found during the preparative reduction at a potential where a phenyldiimide (**94**) would be expected to give a wave, the following reduction route was suggested.



<sup>96</sup> S. Kwee and H. Lund, *Electrochem. Soc. Meeting, New York, 1969. Extended Abstr.* p. 349.

<sup>97</sup> H. Lund, to be published.

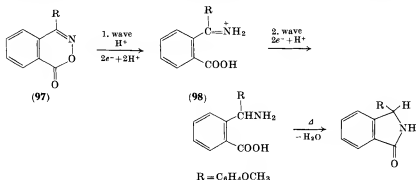
A somewhat similar result<sup>97</sup> is obtained in the reduction of 4-methyl-1,2,3-benzotriazine-3-oxide (**94**) to 3-methylindazole (**95**) and hydroxylamine by a four-electron reduction. At pH 4 **94** gives two four-electron waves; the second wave is probably caused by the reduction of the intermediate oxime (**96**). Both waves disappear during the electrolysis at the potential of the first wave (Scheme 11).



SCHEME 11

## 2. Hydrogenolysis of a Nitrogen-Oxygen Bond

The initial step in the reduction of protonated oximes has been shown<sup>91</sup> to be a hydrogenolysis of the nitrogen-oxygen bond; in cyclic derivatives of oximes the same occurs. In 4-(4'-methoxyphenyl)-2,3-benzoxazin-1-one (**97**) the reduction proceeds in two steps and it is possible to isolate the rather stable intermediate ketimine (**98**).<sup>98</sup>

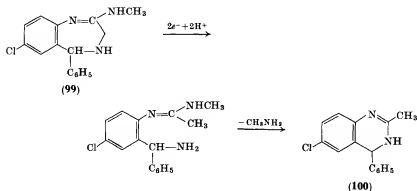


<sup>98</sup> H. Lund, *Acta Chem. Scand.* **18**, 563 (1964).

### 3. Hydrogenolysis of Nitrogen-Carbon Bond

An electrolytic cleavage of such a bond in a convenient potential interval occurs only when the bond is activated, e.g., by an adjacent carbonyl or azomethine group.

A ring contraction occurs during the reduction of 7-chloro-2-methylamino-5-phenyl-3*H*-4,5-dihydro-1,4-benzodiazepine (**99**) to 6-chloro-2-methyl-4-phenyl-3,4-dihydroquinazoline (**100**).<sup>99</sup> It has been suggested that the reaction takes the course shown in Scheme 12,<sup>61</sup> but another interpretation has also been offered.<sup>99</sup>



### C. RING EXPANSIONS

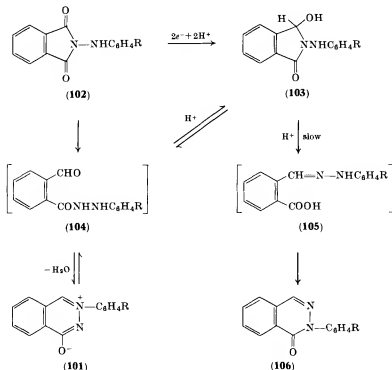
Only a few types of ring expansion involving electrolysis have been reported so far. In the preparation of  $\psi$ -phthalazinones (**101**) from *N*-anilinothalimides (**102**),<sup>100</sup> the phthalimide derivative is reduced to a derivative of phthalaldehydic acid, *N*-anilinohydroxyphthalimidine (**103**). It has been suggested<sup>61, 101</sup> that this compound undergoes a ring opening to a hydrazide of phthalaldehydic acid (**104**). On ring closure the more nucleophilic nitrogen of the hydrazide attacks the aldehyde group with formation of a six-membered ring. In strongly acid solution the  $\psi$ -phthalazinone ring may be opened again as

<sup>99</sup> H. Oelschläger and H. Hoffmann, *Arch. Pharm.* **300**, 817 (1967).

<sup>100</sup> H. Lund, *Tetrahedron Letters* 3973 (1965).

<sup>101</sup> W. R. Vaughan, D. I. McCane, and G. J. Sloan, *J. Am. Chem. Soc.* **73**, 2298 (1951).

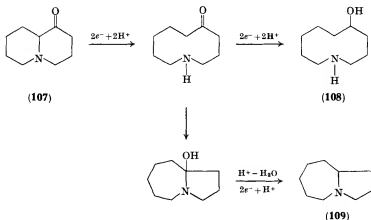
suggested below and then some of the hydroxyphthalimidine (**103**) forms a phenylhydrazone of phthalaldehydic acid (**105**) on hydrolytic ring opening. The phenylhydrazone would on ring closure yield 2-phenylphthalazinone (**106**); this Rowe rearrangement<sup>101</sup> can thus be explained by assuming that the  $\psi$ -(3-aryl)phthalazinone is the kinetically controlled product, whereas the 2-arylphthalazinone is the thermodynamically controlled product.



A special type of ring enlargement is found in the electrolytic reduction of bicyclic  $\alpha$ -aminoketones (lead cathode, 30% sulfuric acid, 60°C) to monocyclic products.<sup>102, 103</sup> Thus, 1-ketoquinolizidine (**107**) under these conditions gave 59% 5-hydroxyazacyclodecane (**108**) and 4.5% 1-azabicyclo[5.3.0]decane (**109**) (Scheme 13).

<sup>102</sup> S. Swann and N. Leonard, *J. Am. Chem. Soc.* **74**, 4620 (1952).

<sup>103</sup> S. Swann and N. Leonard, *J. Am. Chem. Soc.* **74**, 6251 (1952).



SCHEME 13

The initial cleavage of the carbon-nitrogen bond is analogous to that found in the reduction of derivatives of 2-aminoacetophenone<sup>104</sup> and to the first step in the ring contraction of **99**.

## V. Electrolytic Reactions of Heterocyclic Systems

In the following chapter the electrode reactions of heterocyclic compounds in which a reduction or oxidation of the nucleus takes place are discussed. Ring systems carrying substituents are included only when the substituent significantly influences the electrode reaction of the nucleus.

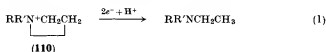
### A. COMPOUNDS WITH ONE NITROGEN ATOM

a. *Aziridinium Compounds.* A nitrogen mustard of the type  $RR'NCH_2CH_2Cl$  is electrolytically reducible<sup>105</sup>; it has been suggested that the reducible species is the self-quaternized product, the aziridinium compound (**110**), and that the electrode reaction is shown in Eq. (1).

b. *Pyrrole Derivatives.* Pyrrole is not polarographically reducible, but can be reduced at a lead cathode in dilute sulfuric acid to pyrroline

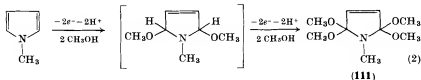
<sup>104</sup> P. Zuman and V. Horak, *Collection Czech. Chem. Commun.* **26**, 176 (1961).

<sup>105</sup> N. G. Lordi and E. C. Olson, *J. Am. Chem. Soc.* **79**, 2697 (1957).



and further to pyrrolidine<sup>106, 107</sup>; under similar conditions 1,2-dimethylpyrroline is also reduced to the pyrrolidine,<sup>108</sup> and indoles to indolines.<sup>109-111</sup> Pyrrole may also be anodically oxidized. Oxidation of pyrrole at a platinum electrode in acetonitrile yields a tar which covers the electrode with an insulating layer<sup>54</sup>; however, electrolysis of pyrrole in acetonitrile in the presence of benzaldehyde yields tetraphenylporphin besides some tar and other side products.<sup>112</sup> The porphin synthesis is initiated by protons formed in the oxidation of pyrrole; condensation of protonated pyrrole molecules with benzaldehyde forms tetraphenylporphinogen which is oxidized to the porphin anodically or by a redox reaction with pyrrole.

In acetonitrile, pentaphenylpyrrole is oxidized to a rather stable cation radical.<sup>113</sup> In methanolic solution 1-methylpyrrole forms 1-methyl-2,2,5,5-tetramethoxypyrroline (111),<sup>114</sup> schematically according to Eq. (2).



Under similar conditions furan is oxidized to dimethoxydihydrofuran and thiophene to dimethoxydihydrothiophene.

c. *Carbazoles*. Carbazoles are oxidized at controlled potential at a platinum anode in acetonitrile to cation radicals which are stable

<sup>106</sup> M. Dennstedt, German Patent 127,086 (1901).

<sup>107</sup> B. Sakurai, *Bull. Chem. Soc. Japan* **11**, 374 (1936).

<sup>108</sup> L. C. Craig, *J. Am. Chem. Soc.* **55**, 2543 (1933).

<sup>109</sup> O. Carrasco, *Gazz. Chim. Ital.* **38**, 301 (1908).

<sup>110</sup> J. von Braun and W. Sobecki, *Ber.* **44**, 2158 (1911).

<sup>111</sup> J. T. Wrobel and K. M. Pazdro, *Roczniki Chem.* **41**, 637 (1967).

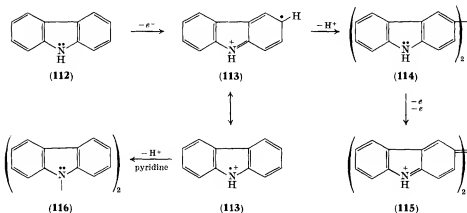
<sup>112</sup> A. Stanienda, *Z. Naturforsch.* **22b**, 1107 (1967).

<sup>113</sup> G. Cauquis and M. Gewies, *Bull. Soc. Chim. France* 3220 (1967).

<sup>114</sup> N. L. Weinberg and E. A. Brown, *J. Org. Chem.* **31**, 4054 (1966).



when the 3-, 6-, and 9-positions are blocked.<sup>115, 116</sup> The radical cation (**113**) from carbazole (**112**) dimerizes predominantly at the 3-position to 3,3'-dicarbazolyl (**114**) which is further oxidizable to the quinonoid dication (**115**) at the potential used. In the presence of pyridine, which may cause a rapid deprotonation of the NH-proton of **113**, 9,9'-dicarbazolyl (**116**) is the isolated product.



d. *Pyridine Derivatives.* Pyridine is not polarographically reducible and only with difficulty oxidizable at a platinum electrode in acetonitrile. It can, however, be reduced to piperidine at a lead cathode in 10%  $H_2SO_4$ .<sup>117, 118</sup> The yield is very dependent on the purity of the lead and other components; side products are  $\alpha, \alpha$ - and  $\gamma, \gamma$ -dipiperidyl.

Substituents may render the nucleus more easily reducible and oxidizable; electron-attracting substituents, e.g., carbethoxy groups, facilitate the reduction, whereas methoxy groups make the oxidation easier. A positive charge on the nitrogen atom also facilitates the reduction of the nucleus, but the charged pyridine ring also makes the electron-attracting substituent more easily reduced; in cases where the electrode reaction changes with pH it is generally the substituent that is reduced in acid and the nucleus in alkaline solution.

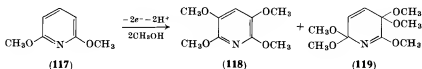
<sup>115</sup> J. F. Ambrose and R. F. Nelson, *J. Electrochem. Soc.* **115**, 1159 (1968).

<sup>116</sup> J. F. Ambrose, L. L. Carpenter, S. C. Creason, and R. F. Nelson, *Electrochem. Soc. Meeting, 1969, Extended Abstr.* p. 354.

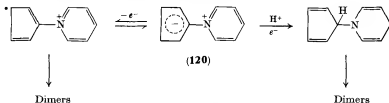
<sup>117</sup> F. B. Ahrens, *Z. Elektrochem.* **2**, 577 (1895).

<sup>118</sup> B. Emmert, *Ber.* **46**, 1716 (1913).

The presence of two methoxy groups on the pyridine ring makes it susceptible to anodic oxidation. In alkaline methanol the main products from 2,6-dimethoxypyridine (**117**) are 2,3,5,6-tetramethoxypyridine (**118**) and an azaquinone derivative, probably having structure **119**.<sup>114</sup>



Pyridinium salts are generally polarographically reducible in alkaline solution and dimerized dihydropyridine derivatives have been postulated as products.<sup>119,120</sup> A special compound of this type is pyridinium cyclopentadienylide (**120**),<sup>121</sup> which gives both an anodic and a cathodic one-electron wave in alkaline solution and in acid solution only a cathodic wave (Scheme 14).



SCHEME 14

Bipyridylium compounds are reduced similarly with one electron per nucleus,<sup>122-124</sup> the "semiquinone" (**121**) having a considerable stability. An attempt has been made to correlate the electrochemical properties of quaternary bipyridylium salts with their herbicidal activity.<sup>125</sup>

<sup>119</sup> P. C. Tompkins and C. L. A. Schmidt, *Univ. California Publ. Physiol.* **8**, 237, 247, (1944).

<sup>120</sup> S. G. Mairanovskii, *Dok. Akad. Nauk. SSSR* **110**, 593 (1956).

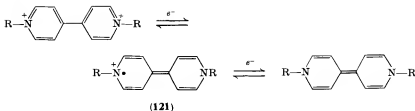
<sup>121</sup> S. I. Zdanov and L. S. Mirkin, *Collection Czech. Chem. Commun.* **26**, 370 (1961).

<sup>122</sup> R. M. Eloffson and R. L. Edsberg, *Can. J. Chem.* **35**, 646 (1957).

<sup>123</sup> G. Gruver, T. Osa, and T. Kuwana, *Symp. Synthetic Mechanistic Aspects Electro-org. Chem., Durham, North Carolina, 1968. Preprints of Papers* p. 1.

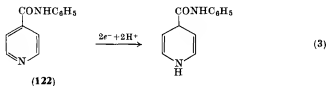
<sup>124</sup> S. Hünig and J. Gross, *Tetrahedron Letters* 2599 (1968).

<sup>125</sup> J. Volke, *Collection Czech. Chem. Commun.* **33**, 3044 (1968).



Electrolysis without potential control of some alkyl pyridines and their quaternary derivatives has yielded a mixture of piperidines and tetrahydropyridines<sup>126</sup> (see the chapter by Ferles and Pliml, this volume, p. 43).

Derivatives of the pyridine carboxylic acids are polarographically reducible both in acid and alkaline solution; in the latter solvent the nucleus is reduced.<sup>127</sup> In the few cases where a macroscale reduction at a mercury electrode<sup>127, 128</sup> has been made, the 1,4-dihydropyridine has been isolated [e.g., Eq. (3)].<sup>127</sup>



The quaternary derivatives of **122** are reduced in 2 one-electron waves in alkaline solution. The green precipitate obtained by a reduction at the potential of the first wave was shown to be a radical by its paramagnetic properties; further reduction produced the 1,4-dihydro derivative.

The reduction of quaternary derivatives of nicotinic amide has been subject to many polarographic<sup>119, 128-133</sup> and electrolytic

<sup>126</sup> M. Ferles and A. Šilhánková, *Z. Chem.* **8**, 175 (1968).

<sup>127</sup> H. Lund, *Acta Chem. Scand.* **17**, 2325 (1963).

<sup>128</sup> J. N. Burnett and A. L. Underwood, *J. Org. Chem.* **30**, 1154 (1965).

<sup>129</sup> F. Šorm and Z. Šormová, *Chem. Listy* **42**, 82 (1948).

<sup>130</sup> S. J. Leach, J. H. Baxendale, and M. G. Evans, *Australian J. Chem.* **6**, 395 (1953).

<sup>131</sup> J. Nakaya, *Nippon Kagaku Zasshi* **81**, 1459 (1960); *Chem. Abstr.* **56**, 4514 (1962).

<sup>132</sup> H. Yasuda and S. Kitagawa, *Yakugaku Kenkyu* **27**, 779 (1955); *Chem. Abstr.* **51**, 13246 (1957).

<sup>133</sup> A. J. Cunningham and A. L. Underwood, *Biochemistry* **6**, 266 (1967).

investigations<sup>128, 130</sup> as model compounds for the phosphopyridine nucleotides. At pH 4-7 a one-electron wave is formed, whereas in alkaline solution 2 one-electron waves are seen. Controlled potential reduction in a phosphate buffer at the potential ( $-1.2$  volts) of the first wave of 1-methyl-3-carbamidopyridinium perchlorate produced a dimer, suggested to be the 6,6'-dimer; at a more negative potential ( $-1.8$  volts) the dimer was reduced further with two electrons per nucleus. If the reduction of the perchlorate was performed at the potential of the second wave ( $-1.8$  volts), the 1,4-dihydro derivative was formed.

Analogous results have been obtained in the electrolysis of the pyridine nucleotides<sup>134-141</sup>; the dimer has, however, been suggested to be a 4,4'-dimer.<sup>139</sup> The coenzyme activity of the reduction product varies with the experimental conditions. Some reductions yielded totally inactive products, whereas others produced partly or fully active material. The highest activity was obtained by an indirect electrolytic reduction of triphosphopyridine nucleotide (TPN).<sup>141</sup> Electrochemical reduction of methyl viologen in the presence of ferredoxin-TPN-reductase caused a reduction of TPN to a biochemically active product.

e. *Quinoline, Isoquinoline, and Acridine.* Quinoline and isoquinoline derivatives are polarographically reducible in a similar way as the pyridine compounds, but the reduction potentials required are generally less negative.

The reduction of quinoline at different electrodes in sulfuric acid to dihydro- and tetrahydroquinoline has been studied using constant current<sup>142, 143</sup>; the reaction is of the type A2 (Section II, A) and proceeds with high current efficiency at electrodes with high hydrogen

<sup>134</sup> B. Ke, *J. Am. Chem. Soc.* **78**, 3649 (1956).

<sup>135</sup> B. Ke, *Arch. Biochem. Biophys.* **60**, 505 (1956).

<sup>136</sup> R. F. Powning and C. C. Kratzing, *Arch. Biochem. Biophys.* **66**, 249 (1957).

<sup>137</sup> T. Kono and S. Nakamura, *Bull. Agr. Chem. Soc. Japan* **22**, 399 (1958); *Chem. Abstr.* **53**, 18120 (1959).

<sup>138</sup> J. N. Burnett and A. L. Underwood, *Biochemistry* **4**, 2060 (1965).

<sup>139</sup> A. J. Cunningham and A. L. Underwood, *Arch. Biochem. Biophys.* **117**, 88 (1966).

<sup>140</sup> R. W. Burnett and A. L. Underwood, *Biochemistry* **7**, 3328 (1968).

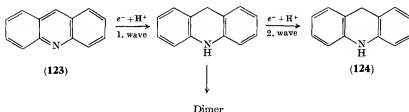
<sup>141</sup> R. J. Day, S. J. Kinsey, E. T. Seo, and H. P. Silverman, *Electrochem. Soc. Meeting, New York, 1969, Extended Abstr.* p. 357.

<sup>142</sup> N. E. Khomutov and V. V. Tsodikov, *Elektrokhimiya* **1**, 482 (1965).

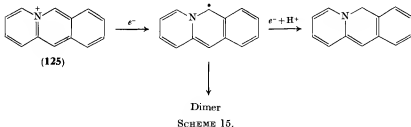
<sup>143</sup> N. E. Khomutov and V. V. Tsodikov, *Elektrokhimiya* **2**, 722 (1966).

overtoltage (e.g., lead), but not at platinum electrodes which have a low hydrogen overvoltage.

Acridine (123) is polarographically reducible both in acid and alkaline solution.<sup>144</sup> In strongly acid solution a single one-electron wave is found, and from a preparative reduction compounds dimerized at C-9 were isolated.<sup>54</sup> In less acid and in alkaline solution 2 one-electron waves are found, the latter probably resulting in 9,10-dihydroacridine (124).



The acridizinium (125) and phenanthridizinium systems are reducible<sup>145</sup> in a similar manner and the two-step reduction found in acid solution is suggested to proceed as in Scheme 15.



## B. COMPOUNDS WITH ONE NITROGEN AND ONE OXYGEN ATOM

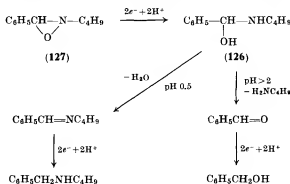
a. *Oxaziridines*. Oxaziridines are very easily reducible compounds and their polarographic wave<sup>146</sup> begins at the dissolution wave of the mercury. In the reduction a *gem*-amino alcohol (126) is formed which

<sup>144</sup> R. C. Kaye and H. I. Stonehill, *J. Chem. Soc.* 27 (1951).

<sup>145</sup> J. G. Frost, and J. H. Saylor, *Rec. Trav. Chim.* **82**, 828 (1963).

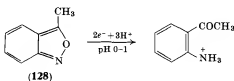
<sup>146</sup> H. Lund, *Acta Chem. Scand.* **23**, 563 (1969).

at low pH loses water with the formation of a Schiff base, and at higher pH loses amine to give a carbonyl compound. The Schiff base or the carbonyl compound may be further reduced. The reduction of 2-*t*-butyl-3-phenyloxaziridine (127) exemplifies this (Scheme 16).



SCHEME 16

b. *Anthranils*. These compounds give in acid solution two polarographic waves, and a reduction at a potential corresponding to the foot of the first wave of 3-methyl-anthranil (128) yields *o*-aminoacetophenone in good yield<sup>61</sup>; the second wave represents the reduction of this compound. In alkaline medium a single three-electron wave is found, and the reaction mixture contains several dimerized compounds.<sup>71</sup>

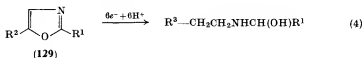


c. *Benzoxazines*. 2,3-Benzoxazin-1-ones are cyclic oximes and are reduced correspondingly; the nitrogen-oxygen bond is hydrogenolyzed before the saturation of the carbon-nitrogen double bond. Their reduction was discussed above (Section IV, B, 2).

d. *Oxazoles*. Aryl-substituted oxazoles (129) are reducible<sup>147</sup> at

<sup>147</sup> V. D. Bezuglyi, N. P. Shimanskaya, and E. M. Peresleni, *Zh. Obshch. Khim.* **34**, 3540 (1964).

rather negative potentials [ $-1.9$  to  $-2.1$  volts (SCE)] and the electrode reaction consumes in most cases six electrons; the reduction is suggested to proceed as follows [Eq. (4)]. This product would be ex-



pected to hydrolyze easily to an amine and the reducible arylaldehyde. The reduction of 2-(1-naphthyl)-5-phenyloxazole consumes two electrons per molecule and the oxazoline has been suggested as the product.<sup>147</sup>

### C. COMPOUNDS WITH ONE NITROGEN AND ONE SULFUR ATOM

a. *Thiazole Derivatives.* Thiazole and its simple alkyl or aryl derivatives are not polarographically reducible, but substitution in the thiazole ring with electron-attracting groups may render the nucleus susceptible. Derivatives of thiazole-2-carboxylic acid are reduced in alkaline solution, and the reduction is assumed to take place in the nucleus, but the products have not been isolated. Although the main reaction in acid solution involves the reduction of the carboxyl group, some reduction of the thiazole ring is also observed.<sup>148</sup>

Many thiazolium salts are polarographically reducible<sup>149, 150</sup>; 3-methylbenzothiazolium iodide<sup>149</sup> (130) is reduced in a two-electron wave, but a preparative reduction gave  $n$  between 1 and 2 and a mixture of a dimer and 2,3-dihydro-3-methylbenzothiazole was found. Aryl groups in the 2-position hinder dimerization.<sup>150</sup>

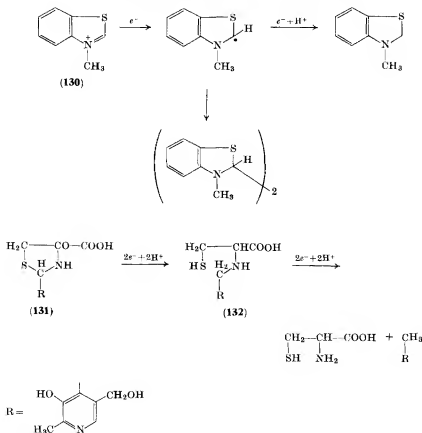
Cleavage of a thiazolidine ring is observed<sup>151</sup> in the reduction of the condensation product between cysteine and pyridoxal, 2-(2-methyl-3-hydroxy-5-hydroxymethyl-4-pyridyl)thiazolidine-4-carboxylic acid (131). The reduction is best understood when the compound is considered as a derivative of 4-pyridine carbaldehyde

<sup>148</sup> P. E. Iversen and H. Lund, *Acta Chem. Scand.* **21**, 389 (1967).

<sup>149</sup> H. Lund, Unpublished results.

<sup>150</sup> Z. N. Timofeeva, M. V. Petrova, M. Z. Girshovich, and A. V. El'tsov, *Zh. Obshch. Khim.* **39**, 54 (1969).

<sup>151</sup> O. Manousek and P. Zuman, *Collection Czech. Chem. Commun.* **29**, 1718 (1964).

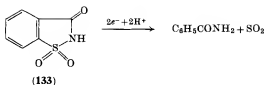


(Section VI, C), and the further reducible intermediate (132), a derivative of 4-pyridylmethanamine (Section VI, E).

b. *Isothiazole Derivatives*. Substituted benzenesulfonamides bearing strongly electron-attracting substituents can be reduced in slightly alkaline solution at the dropping mercury electrode to ammonia, sulfur dioxide, and a monosubstituted benzene.<sup>152</sup> Saccharin (133) is a compound of this type and the primary electrode reaction is a cleavage of the carbon-sulfur bond; chemical reactions follow the initial cleavage.

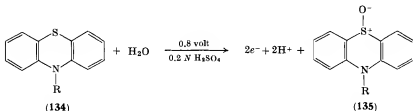
<sup>152</sup> O. Manousek, O. Exner, and P. Zuman, *Collection Czech. Chem. Commun.* **33**, 4000 (1968).





In acid solution the reduction follows a similar route as that of phthalimide, with a primary reduction of the carbonyl group<sup>153, 154</sup> (Section VI, B).

c. *Thiazines*. Simple thiazines have not been investigated polarographically. Several derivatives of phenothiazine (134) have been found to be oxidizable at a gold anode in dilute sulfuric acid.<sup>155</sup> The product proved to be the sulfoxide (135) rather than the *N*-oxide.



#### D. COMPOUNDS WITH TWO NITROGEN ATOMS

a. *Diazirines*. Diazirines (e.g., 136) are polarographically reducible in acid solution in a four-electron reduction and in alkaline medium in a two-electron reaction.<sup>156</sup> Diaziridines (137) are reducible only in acid solution<sup>157</sup>; in alkaline solution they can be oxidized anodically to diazirines.<sup>156</sup> The reactions of 3,3-pentamethylenediazine (136) can be formulated as in Scheme 17.

The protonated diaziridine (138) is more easily reducible than the diazine which is too weakly basic to be protonated in aqueous solution. In alkali, where both are unprotonated, the diazine is the

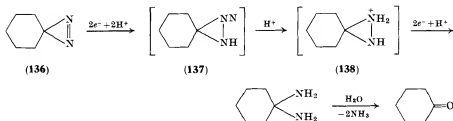
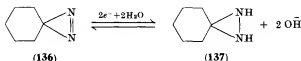
<sup>153</sup> M. Matsui, T. Sawamura, and T. Adachi, *Mem. Coll. Sci. Kyoto Imp. Univ.* **15A**, 151 (1932); *Chem. Abstr.* **26**, 5264 (1932).

<sup>154</sup> H. Lund, Unpublished observation.

<sup>155</sup> P. Kabasakalian and J. Mc. Glotten, *Anal. Chem.* **31**, 431 (1959).

<sup>156</sup> H. Lund, *Collection Czech. Chem. Commun.* **31**, 4175 (1966).

<sup>157</sup> J. P. Kitaev and G. K. Budnikov, *Collection Czech. Chem. Commun.* **30**, 4178 (1965).

*Acid solution**Alkaline solution*

SCHEME 17

easier to reduce. This explains why it has been difficult to obtain good yields of diaziridine by chemical and catalytic reduction of a diazine; for such a reduction to result in a high yield of diaziridine it must be performed in an alkaline medium.

b. *Benzimidazoles*. Benzimidazoles (139) are generally not polarographically active, but some of the reduced derivatives may be. The condensation products of *o*-phenylenediamine with glycolaldehyde



and glyceraldehyde, which are benzimidazolines, give an anodic polarographic wave which probably is due to a two-electron oxidation to a benzimidazole derivative.<sup>158</sup>

c. *Pyridazines*. Pyridazines are polarographically reducible,<sup>159, 160</sup> often stepwise. The first reduction generally yields a dihydropyridazine which can exist in different tautomeric forms, the most stable forms usually being the 1,4- and 4,5-dihydropyridazine. Further reduction

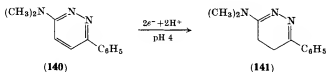
<sup>158</sup> T. Wasa and S. Musha, *Bull. Chem. Soc. Japan* **40**, 1624 (1967).

<sup>159</sup> H. Lund, *Oesterr. Chemiker-Z.* **68**, 43 (1967).

<sup>160</sup> S. Millefiori, *Ann. Chim. (Rome)* **59**, 15 (1969).

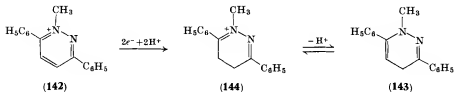
is complicated by the fact that the different tautomeric forms may be reduced differently and at different potentials and that the rate of transformation of a given tautomer to the most easily reducible one may or may not be fast compared with the further reduction.

Reduction in acetate buffer at the potential of the first wave of 3-phenyl-6-dimethylaminopyridazine (**140**) yields the 4,5-dihydro-derivative (**141**) in high yield.<sup>159</sup>



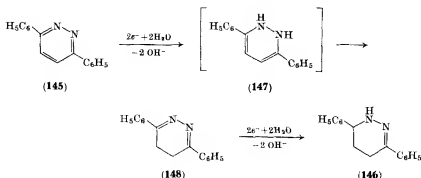
In a similar way other pyridazines,<sup>159</sup> e.g., 3-phenyl-6-methoxy-pyridazine and 3-methyl-6-chloropyridazine, are reduced, but the dihydropyridazines are in these cases rather unstable and may lose methanol or hydrogen chloride forming the corresponding 4,5-dihydropyridazinone. The reduction of pyridazinones will be discussed below.

The product isolated<sup>159</sup> from the two-electron reduction of 1-methyl-3,6-diphenylpyridazinium iodide (**142**) in acid solution after extraction from neutral solution was 1,4-dihydro-1-methyl-3,6-diphenylpyridazine (**143**); however, as it has been found that 1,4-dihydro-3,6-diphenylpyridazine in trifluoroacetic acid is transformed into the 4,5-dihydroderivative (**144**),<sup>94</sup> this tautomer might be the predominant one in the acid solution.



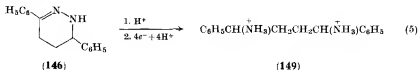
In alkaline solution 3,6-diphenylpyridazine (**145**) gives a two-electron polarographic wave which in strongly alkaline solution is followed closely by a smaller wave. A preparative reduction at the potential of the second wave yielded 3,6-diphenyl-2,3,4,5-tetrahydropyridazine (**146**). It has been suggested<sup>94</sup> that the primary

reduction product is a 1,2-dihydropyridazine (147) which tautomerizes to the 4,5-dihydro derivative (148); this compound is then reduced further, analogously to the reduction of benzalazine.<sup>91</sup>

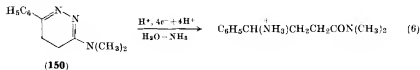


The reduction in acid solution of di- and tetrahydropyridazines is often best understood when their resemblance to hydrazones is considered; the reduction of such compounds has been briefly discussed in Section IV, B, and the primary step is a hydrogenolysis of the nitrogen-nitrogen bond. The reduction of 1,4-dihydro-1-methyl-5-*t*-butyl-3,6-diphenylpyridazine was also described above (Section IV, B).

Compound 146 is structurally similar to a benzylhydrazone of propiophenone and, in accordance with that, a four-electron polarographic wave is observed in acid solution with formation of 149.<sup>159</sup> The electrode reaction is shown in Eq. (5).



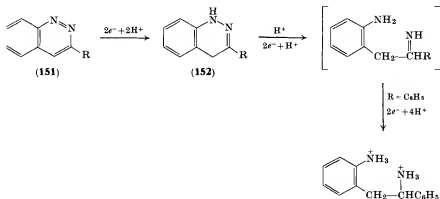
In a similar way 4,5-dihydro-3-dimethylamino-6-phenylpyridazine (150) is reduced [Eq. (6)].



3,6-Diphenyldihydropyridazine, which in acid solution is probably present as the 4,5-dihydro derivative, is reduced differently from what would be expected based on its similarity to benzalazine since dimeric compounds are the main products.

d. *Cinnolines*. Cinnolines are generally reducible<sup>141</sup> in two or more steps. The first step in the reduction of aryl- or alkyl-substituted cinnolines (151) is the formation of 1,4-dihydrocinnolines; this reduction is not reversible. Only in the case of benzo[*c*]cinnoline is the reduction a saturation of the nitrogen-nitrogen double bond. The reaction resembles the reduction of azobenzene to hydrazobenzene and like this system is polarographically nearly reversible.<sup>141</sup>

1,4-Dihydrocinnolines may be regarded as cyclic phenylhydrazones and their reduction is in accordance with that; only the protonated compounds are reducible, and the first two-electron step produces an amine and an imine. If the imine is reducible at the potential necessary for the hydrogenolysis of the nitrogen-nitrogen bond, the imine is reduced to an amine; if not, ring closure to an indole takes place, unless the potential is kept so negative that the further reduction of the imine can compete with the ring closure. The ring contraction to indoles has been discussed in Section IV, B. The reduction of 1,4-dihydro-3-phenylcinnoline (152) proceeds by a four-electron reaction.

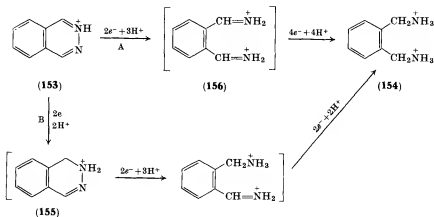


A similar reduction of the isomeric quaternized *N*-methyl-3-phenylcinnolinium compounds has been used as one of the arguments

<sup>141</sup> S. D. Ross, G. J. Kahan, and W. A. Leach, *J. Am. Chem. Soc.* **74**, 4122 (1952).

for a predominant quaternization of 3-phenylcinnoline (**151**, R = Ph) at N-1.<sup>144, 162</sup>

e. *Phthalazines*. These compounds in acid solution are reduced somewhat differently from cinnolines. In acid phthalazine (**153**) is reduced polarographically in a six-electron wave,<sup>93</sup> presumably to *o*-xylene- $\alpha, \alpha'$ -diamine (**154**), but in a preparative reduction 6 *N* hydrochloric acid<sup>94</sup> is required as medium if the diamine is the desired product.



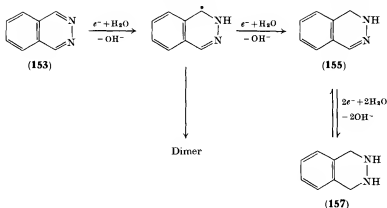
Whether reaction route A or B (or both) operates is not yet known because both 1,2-dihydrophthalazine (**155**) and the aldimine (**156**) are reduced at a less negative or approximately the same potential as **153**. The reduction of **153** thus resembles the reduction of benzalazine.

In alkaline solution **153** is reduced polarographically in a two-electron reduction, but under preparative conditions it is possible to isolate mostly dimerized products resulting from a one-electron reduction, or **155**, depending on the conditions. A more negative potential gives 1,2,3,4-tetrahydrophthalazine (**157**) which might be oxidized anodically to **155**. The electrolytic method thus is advantageous for the preparation of **155**.<sup>159, 163</sup>

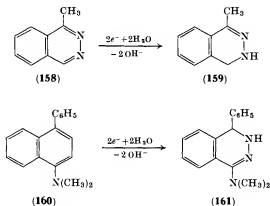
The reduction course of substituted phthalazines depends on the substituents. Thus, 1-methylphthalazine (**158**) in alkaline solution

<sup>162</sup> D. E. Ames, B. Novitt, D. Waite, and H. Lund, *J. Chem. Soc. C* 796 (1969).

<sup>163</sup> H. Lund, *Lecture 12th Nord. Kemikermoeede, Trondheim, 1965, Abstr. of Papers* p. 33.



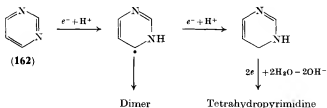
forms 1-methyl-3,4-dihydrophthalazine (159), whereas 1-phenyl-4-dimethylaminophthalazine (160) is reduced to 1,2-dihydro-1-phenyl-4-dimethylaminophthalazine (161). The reduction of these compounds in acid solution has been discussed above.



f. *Pyrimidines*. In acid solution pyrimidine (162)<sup>164, 165</sup> is reduced polarographically in 2 one-electron waves; 2 two-electron waves are observed in neutral medium, whereas a four-electron reduction occurs in alkaline solution. These findings have been interpreted according to Scheme 18.

<sup>164</sup> D. L. Smith and P. J. Elving, *J. Am. Chem. Soc.* **84**, 2741 (1962).

<sup>165</sup> B. Janik and P. J. Elving, *Chem. Rev.* **68**, 295 (1968).

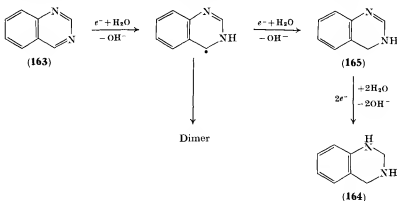


SCHEME 18

The structure of the tetrahydropyrimidine has not been determined. 2-Aminopyrimidine is reduced similarly, but the dihydropyrimidine is not further reducible.

g. *Quinazoline*. The polarographic behavior of quinazoline (163)<sup>166</sup> is complicated by the hydration of the quinazolinium ion. The hydrated cation is not reducible, and in the acid region the wave height is partly determined by the rate of its dehydration, and this has been used to find the rate of its dehydration at different pH values.<sup>166</sup>

The reduction of 163 resembles that of 162; in alkaline solution it is reduced stepwise to the 1,2,3,4-tetrahydroquinazoline (164).



h. *Pyrazine, Quinoxaline, and Phenazine*. Pyrazine and its reduction product, 1,4-dihydropyrazine, form a system which at a mercury electrode behaves nearly reversibly.<sup>167, 168</sup> In acid solution 2

<sup>166</sup> H. Lund, *Acta Chem. Scand.* **18**, 1984 (1964).

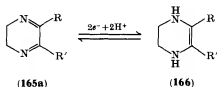
<sup>167</sup> L. F. Wiggins and W. S. Wise, *J. Chem. Soc.* 4780 (1956).

<sup>168</sup> J. Volke, D. Dumanovic, and V. Volkova, *Collection Czech. Chem. Commun.* **30**, 246 (1965).



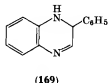
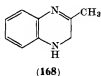
one-electron waves are found indicating a certain stability of the semiquinone-like one-electron reduction product.

The electrochemical reduction of 2,3-disubstituted 5,6-dihydropyrazines (**165a**) yields the 1,4,5,6-tetrahydropyrazines (**166**)<sup>169</sup>; the diimine-enediamine system is thus analogous to the dione-enediol system. It is of interest that the 5,6-dihydropyrazines are somewhat more easily reduced than the pyrazines.



Quinoxaline<sup>170-172</sup> is reduced to 1,4-dihydroquinoxaline (**167**) in a reversible reaction. 2-Methylquinoxaline is reduced to 3,4-dihydro-2-methylquinoxaline (**168**),<sup>172</sup> whereas 2-phenylquinoxaline forms 1,2-dihydro-2-phenylquinoxaline (**169**); the 1,4-dihydroquinoxalines may be formed primarily, but are then tautomerized to the more stable dihydroquinoxaline. 2,3-Diphenylquinoxaline is reduced to *cis*-1,2,3,4-tetrahydro-2,3-diphenylquinoxaline, the 1,4-dihydro compound is transformed into the 1,2-dihydro derivative, which is further reducible.<sup>172</sup>

In aqueous alkaline solution a dimeric product is formed on reduction of quinoxaline besides the 1,4-dihydro compound; on acidification it dissociates.<sup>173</sup>



<sup>169</sup> J. Pinson and J. Armand, *Compt. Rend.* **C266**, 1081 (1968).

<sup>170</sup> G. Sartori and C. Furlani, *Ann. Chim. (Rome)* **45**, 251 (1955).

<sup>171</sup> M. P. Strier and J. C. Cavagnol, *J. Am. Chem. Soc.* **80**, 1565 (1958).

<sup>172</sup> J. Pinson and J. Armand, *Compt. Rend.* **C268**, 629 (1969).

<sup>173</sup> H. Lund, Unpublished observation.

The reduction of phenazine (170) to 5,10-dihydrophenazine is very nearly reversible at the dropping mercury electrode, and its "semi-quinone" has considerable stability.<sup>174-177</sup>

5,10-Dihydro-5,10-dimethylphenazine (171) exhibits two successive reversible one-electron oxidation steps in acetonitrile (Fig. 9) or propylene carbonate as solvents.<sup>178</sup> When the compound is electrolyzed in a more nucleophilic solvent, however, the second oxidation is

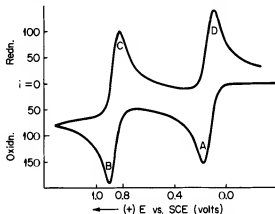
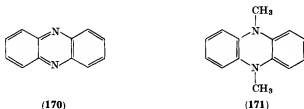


Fig. 9. Cyclic polarogram of 5,10-dihydro-5,10-dimethylphenazine ( $2.0 \times 10^{-3} M$ ) in acetonitrile; platinum electrode, 0.1 *M* tetraethylammonium perchlorate as supporting electrolyte, scan rate 5.0 volts/min. The anodic peaks A and B are caused by the formation of the mono- and dication, respectively, and the cathodic peaks D and C by the reduction of these cations. From Nelson *et al.*<sup>178</sup>



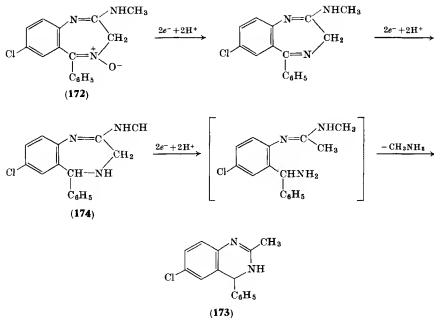
<sup>174</sup> O. N. Nechaeva and Z. V. Pushkareva, *Zh. Obshch. Khim.* **28**, 2693 (1958).

<sup>175</sup> L. V. Varyukhina and Z. V. Pushkareva, *Zh. Obshch. Khim.* **26**, 1740 (1956).

<sup>176</sup> L. L. Gordienko, *Elektrokhimiya* **1**, 1497 (1965).

<sup>177</sup> R. Curti, S. Locchi, and V. Landini, *Ric. Sci.* **24**, 2053 (1954).

<sup>178</sup> R. F. Nelson, D. W. Leedy, E. T. Seo, and R. N. Adams, *Z. Anal. Chem.* **224**, 184 (1967).



SCHEME 19

followed by a rapid chemical demethylation. The mechanism of the nucleophilic attack on the dication is not known.

i. *Naphthyridines*. 1,5-Naphthyridine is polarographically reducible at all pH values; macroscale reductions consume approximately one electron per molecule and point to a dimerization<sup>179</sup>; the structures of the products have not been established. The diquaternary salt of 1,5-naphthyridine is polarographically reducible,<sup>180</sup> and other naphthyridines would also be expected to be reducible.

j. *Benzodiazepines*. Both 1,4-<sup>181-184</sup> and 1,5-benzodiazepines<sup>179</sup> are

<sup>179</sup> H. Lund, Unpublished observation.

<sup>180</sup> L. A. Summers and J. E. Dickeson, *Chem. Commun.* 1183 (1967).

<sup>181</sup> H. Oelschläger, *Arch. Pharm.* **296**, 396 (1963).

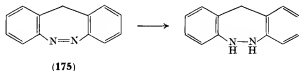
<sup>182</sup> B. Z. Senkowski, M. S. Levin, J. R. Urbigkit, and E. G. Wollish, *Anal. Chem.* **36**, 1991 (1964).

<sup>183</sup> H. Oelschläger, J. Volke, and H. Hoffmann, *Collection Czech. Chem. Commun.* **31**, 1264 (1966).

<sup>184</sup> H. Oelschläger, J. Volke, H. Hoffmann, and E. Kurek, *Arch. Pharm.* **300**, 250 (1967).

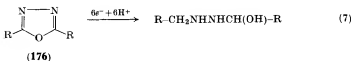
polarographically reducible; the electrode reactions of the former have been elucidated. 7-Chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine-4-oxide (**172**) is reducible in acid solution in three steps. The first two steps, the reduction of the *N*-oxide and the saturation of the benzophenone imine, are straightforward; the mechanism of the third step with ring contraction to a dihydroquinazoline (**173**) is more controversial (Scheme 19). This mechanism seems preferable to one in which the saturation of the C=N in the cyclic amidines (**174**) is the primary step<sup>99</sup> (see Section IV, B, 3).

Dibenzo[*c,f*]-1,2-diazepines (**175**) are also polarographically reducible; the 11-keto<sup>185</sup> and the 4,9-dimethylamino (**61**)<sup>69</sup> derivatives have been investigated and in both cases the N-N double bond is first reduced.



#### E. COMPOUNDS WITH TWO NITROGEN AND ONE OXYGEN ATOM

a. *Oxadiazoles*. Aryloxadiazoles (**176**)<sup>147</sup> are reducible at rather negative potentials; both four- and six-electron reactions are found, sometimes as two-step reductions. The four-electron reduction of symmetrical diaryloxadiazoles has been suggested to produce the oxadiazolidines, whereas the six-electron reduction is believed<sup>147</sup> to proceed as in Eq. (7).

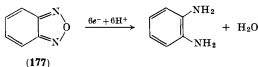


Both the oxadiazolidines and the six-electron reduction product would be expected to hydrolyze easily; the published experimental data do not exclude other interpretations.

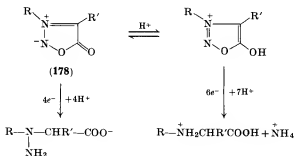
b. *Benzofurazan*. This compound (**177**) is polarographically reducible

<sup>185</sup> R. B. Johns and K. R. Markham, *J. Chem. Soc.* 3712 (1962).

over the whole pH region in a six-electron reaction,<sup>186</sup> and the product is supposedly *o*-phenylenediamine. At a macroelectrode some condensation side reactions might be expected to occur in acid solution as found in the reduction of *o*-dinitrobenzene.<sup>75</sup>



c. *Sydnones*. 3-Phenylsydnones (178) are polarographically reducible both in acid and alkaline medium; in the former six electrons are consumed per molecule, whereas  $n=4$  at high pH. The reactions follow Scheme 20.<sup>187</sup>



SCHEME 20

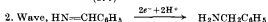
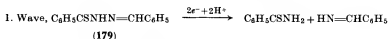
## F. COMPOUNDS WITH TWO NITROGEN AND ONE SULFUR ATOM

a. *1,3,4-Thiadiazoles*. Thiadiazoles are often polarographically reducible<sup>94, 188</sup>; not many of them have been investigated by controlled potential electrolysis. The wave height of 2,5-diphenyl-1,3,4-thiadiazole corresponds in acid solution to a two-electron reduction to a dihydro derivative, which probably is hydrolyzed to benzaldehyde thiobenzoylhydrazone (179). This compound is reducible at the reduction potential of the thiadiazole and will thus be reduced further. Compound 179 is reduced as follows:<sup>94</sup>

<sup>186</sup> R. Schindler, H. Will, and L. Holleck, *Z. Elektrochem.* **63**, 596 (1959).

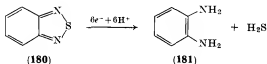
<sup>187</sup> P. Zuman, *Collection Czech. Chem. Commun.* **25**, 3245 (1960).

<sup>188</sup> F. F. Medovshchikova and I. Ya. Postovskii, *Zh. Obshch. Khim.* **24**, 1989 (1954).



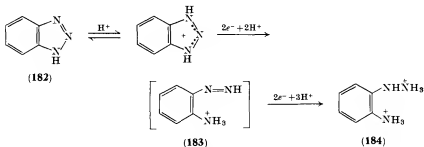
3. Wave, reduction of thiobenzamide

b. *Benzo-2,1,3-thiadiazoles (Piazthioles)*. These compounds (180) and the corresponding selenadiazoles are reduced,<sup>189, 190</sup> like the furazans (177), in a six-electron reaction, to *o*-phenylenediamine (181) and hydrogen sulfide or hydrogen selenide.



#### G. COMPOUNDS WITH THREE NITROGEN ATOMS

a. *Benzotriazoles*. Benzotriazoles (182) are reducible in acid solution, but only 2-substituted derivatives have been found to be reducible in alkaline solution. In acid the following scheme has been proposed.<sup>88</sup>

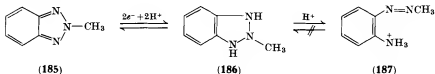


The *o*-aminophenyldiimide (183) cannot be isolated as it is more easily reduced than the benzotriazole, but a small concentration of it can be detected polarographically during the electrolytic reduction. *o*-Aminophenyldihydrazine (184) has three nucleophilic centers and it may be a useful intermediate in heterocyclic synthesis.

<sup>189</sup> L. S. Efros and Z. V. Todres, *Zh. Obshch. Khim.* **27**, 983 (1957).

<sup>190</sup> V. Sh. Tsveniasvili, S. I. Zdanov, and Z. V. Todres, *Z. Anal. Chem.* **224**, 389 (1967).

In alkaline solution 2-methylbenzotriazole (185) is reduced to the 1,3-dihydro derivative which may be reoxidized anodically to the starting material.<sup>88</sup> In acid solution the dihydrobenzotriazole (186) forms an *o*-amino-azo compound (187); this does not cyclize in alkaline solution.



b. *Benzotriazines*. Benzo-1,2,4-triazines and dihydrobenzotriazines form a redox system which polarographically behaves nearly reversibly.<sup>70, 94</sup> The further reduction of the dihydrobenzotriazines to benzimidazoles has been discussed above (Section IV, B, 1); 3-alkyl-substituted dihydrobenzotriazines are generally not further reduced polarographically, but the unsubstituted and 3-phenyl-substituted derivatives are.

Other triazanaphthalenes would be expected to be reducible and the position of the nitrogen atoms to be the deciding factor for the reduction potential. No such data are available yet, however, and reversible hydration of the cations may complicate their polarographic behavior.

#### H. COMPOUNDS WITH FOUR NITROGEN ATOMS

The more nitrogen atoms that are inserted in an aromatic nucleus, the more easily reducible the system becomes. When a heteroaromatic system has two (or more) nitrogen atoms in a six-membered ring, the compound will be reducible, at least in acid solution, and if two nitrogen atoms occupy para positions in such a ring, the redox system will approach reversibility.

a. *Tetrazolium Salts*. Triphenyltetrazolium salts (188) have been investigated polarographically by several workers<sup>191-194</sup>; in acid solution a four-electron reduction is found at 15°C growing to a six-electron wave at 40°C.<sup>194</sup> In alkaline solution 2 two-electron waves

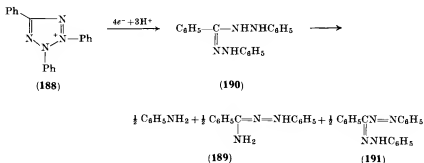
<sup>191</sup> B. Jambor, *Acta Chim. Acad. Sci. Hung.* **4**, 55 (1954).

<sup>192</sup> B. Jambor, *J. Chem. Soc.* 1604 (1958).

<sup>193</sup> H. Campbell and P. O. Kane, *J. Chem. Soc.* 3130 (1956).

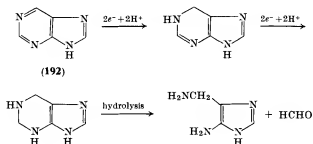
<sup>194</sup> P. Kivalo and K. K. Mustakallio, *Suomen Kemistilehti* **B29**, 154 (1956); **B30**, 214 (1957).

are found. The interpretation of the waves is complicated by adsorption phenomena. As phenylbenzamidrazone (189)<sup>54</sup> is isolated from reduction in acid solution, it has been suggested that the diphenylbenzhydrazidine which is primarily formed (190) disproportionates into phenylbenzamidrazone, aniline, and the reducible triphenylformazan (191).



In alkaline solution triphenylformazan is formed in the first reduction. This compound may be oxidized anodically at a platinum electrode in acetonitrile to triphenyltetrazolium perchlorate.<sup>54</sup>

b. *Purine*. The electrolytic reduction of purine (192)<sup>195</sup> which has recently been reviewed<sup>195</sup> takes place only in acid solution and thus differs from that of pyrimidine and quinazoline. The reduction proceeds in acid solution in 2 two-electron steps according to Scheme 21.<sup>195</sup>



SCHEME 21

<sup>195</sup> D. L. Smith and P. J. Elving, *J. Am. Chem. Soc.* **84**, 1412 (1962).

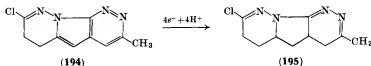


c. *Pteridine*. The polarography of this compound (**193**) is complicated by its instability in aqueous solution.<sup>196</sup> The hydration of the pyrimidine nucleus is followed by ring opening in acid. In neutral solution the compound is reasonably stable; the height of the wave corresponds to a two-electron reduction. The reduction would be expected to occur in the pyrazine ring, and such a reduction would affect the hydration of the pyrimidine ring.



(193)

d. *Dipyridazinopyrrole*. Of such compounds only few have been investigated.<sup>197</sup> The controlled potential reduction of **194** to the tetrahydro derivative (**195**) was a key step in the elucidation of the structure of **194**, as the NMR spectrum of **195** conclusively showed that the nitrogen atoms were placed in the positions shown.



(194)

(195)

e. *Porphins*. The polarographic and controlled potential reduction of porphins (**196**) has been investigated and it was shown that porphin was reduced polarographically in 2 two-electron steps.<sup>198-201</sup> Reduction of mesoporphyrin dimethyl ester yielded a product which was reoxidized easily by oxygen; from the UV spectrum of the solution, which had been reduced in deuterium oxide, it could be shown that the reduction yielded a phlorin (**197**) rather than a chlorin (**198**). Reduction of a chlorin yielded a "chlorin-phlorin."

<sup>196</sup> J. Komenda and D. Laskafeld, *Collection Czech. Chem. Commun.* **27**, 199 (1962).

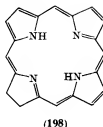
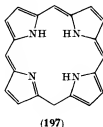
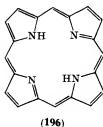
<sup>197</sup> H. Lund and S. Gruhn, *Acta Chem. Scand.* **20**, 2637 (1966).

<sup>198</sup> H. H. Inhoffen and P. Jäger, *Tetrahedron Letters* 1317 (1964).

<sup>199</sup> H. H. Inhoffen and P. Jäger, *Tetrahedron Letters* 3387 (1965).

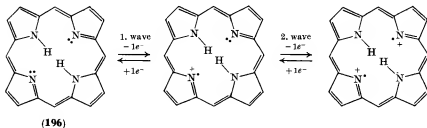
<sup>200</sup> H. H. Inhoffen and R. Mählich, *Tetrahedron Letters* 4283 (1966).

<sup>201</sup> H. H. Inhoffen, P. Jäger, R. Mählich, and C.-D. Mengler, *Ann.* **704**, 188 (1967).



In dimethylformamide porphins are reduced in 3 or 4 one-electron steps which results in formation of mono-, di-, tri-, or tetranegative ions.<sup>202</sup>

Anodic oxidation of porphin in alkyl nitriles at a platinum electrode takes place in 2 one-electron steps.<sup>203</sup> The loss of electrons occurs from the lone pairs on the nitrogen atoms according to Scheme 22.



SCHEME 22

## VI. Electrolysis of Substituted Heterocycles

In this Section we shall consider the electrolysis of substituted heterocyclic compounds, where the electrode reaction involves the substituent directly, or when it plays an essential role in determining the course of the reaction. The reductions leading to ring contractions have been discussed in Section IV, and some compounds treated in Section V might well have been included in Section VI.

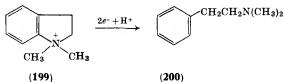
<sup>202</sup> D. W. Clack and N. S. Hush, *J. Am. Chem. Soc.* **87**, 4238 (1965).

<sup>203</sup> A. Stanienda and G. Biebl, *Z. Physik. Chem. (Frankfurt)* **52**, 254 (1967).

## A. ALKYL, ALKENYL, AND ALKYNYL SUBSTITUENTS

a. *Alkyl Substituents.* C-Alkylation of heterocyclic compounds does not change their electrode reactions significantly; the compounds become a little more difficult to reduce or easier to oxidize due to the electron-donating power of the alkyl groups. *N*-Alkylation with quaternization has a more drastic influence; the positive center attracts electrons and the uptake of electrons by the molecule is facilitated. The same is the case for the protonated molecule, but the quaternary compound retains the positive charge at high pH, unless it is attacked by a nucleophile present (e.g.,  $\text{OH}^-$ ), and thus may be reducible in this medium. Some examples of reduction of quaternized heteroaromatic compounds have been mentioned in Section V, C.

Electrolysis in dry liquid ammonia (sodium iodide as supporting electrolyte, Pt electrode) of certain quaternary derivatives of partly reduced heterocyclic systems produces ring cleavage; thus the methiodide of *N*-methylindoline (199) gives 1-phenyl-2-dimethyl-aminoethane (200) in 75% yield.<sup>204, 205</sup>



Cyclic enammonium salts such as 201 are reducible at intermediate pH and in nonaqueous solvents.<sup>206</sup> Electrolysis of 201 at a mercury cathode produced an intermediate (202), which either hydrolyzed to 203 or was reduced further to a mixture of the two isomers of 204. The ratio of these two isomers depended on pH.

Cyclic immonium salts such as 205 are reduced in a nonaqueous solvent such as acetonitrile through a radical to a dimer (206).<sup>207</sup> The reaction is analogous to pinacol formation from carbonyl compounds.

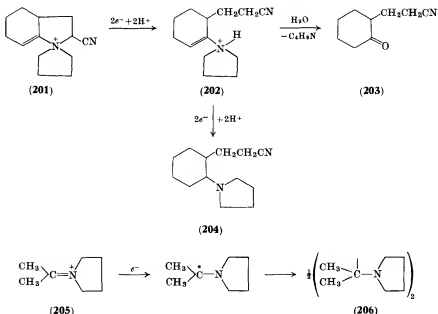
b. *Alkenyl Substituents.* Hydrodimerization of activated alkenes is a well-established process; the hydrodimerization of acrylonitrile to

<sup>204</sup> J. T. Wrobel, K. M. Pazdro, and A. S. Bien, *Chem. Ind. (London)* 1759 (1966).

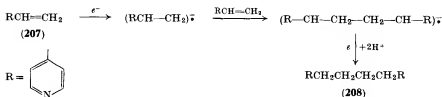
<sup>205</sup> J. T. Wrobel and A. R. Krawczyk, *Chem. Ind. (London)* 656 (1969).

<sup>206</sup> P. E. Iversen and J. Ø. Madsen, Unpublished results.

<sup>207</sup> C. P. Andrieux and J.-M. Saveant, *Bull. Soc. Chim. France* 4671 (1968).



adiponitrile is of great commercial interest.  $\pi$ -Electron-deficient heteroaromatic compounds activate a double bond in a similar way as does a cyano or carbethoxy group, and so vinylpyridines can be hydrodimerized. 4-Vinylpyridine (207)<sup>208</sup> forms 1,4-bis(4-pyridyl)butane (208) in 82% yield on electrolysis in a mildly alkaline solution containing methyltriethylammonium *p*-toluenesulfonate and some dimethylformamide (DMF).



The process is believed<sup>209</sup> to proceed through an anion radical which attacks the substrate rather than through a dimerization of

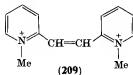
<sup>208</sup> J. D. Anderson, M. M. Baizer, and E. J. Prill, *J. Org. Chem.* **30**, 1645 (1965).

<sup>209</sup> J. F. Petrovich, M. M. Baizer, and M. R. Ort, *Meeting, Electrochem. Soc., New York, 1969, Extended Abstr. p. 335.*

radicals. In the presence of other activated olefins, e.g., dibutyl maleate, cross-coupled products may be obtained.

If the nucleus contains more than one nitrogen atom, the nucleus would be reduced at a less negative potential than the double bond; no reports of electrolysis of such compounds have been published yet.

Quaternization of 1,2-dipyridylethylenes<sup>124</sup> gives diquaternary salts (e.g., **209**) which are reduced in two one-electron steps just as the diquaternary salts of dipyriddy.



c. *Ethynylpyridines*. Ethynylpyridines are reducible polarographically<sup>210</sup> in a medium containing tetraethylammonium iodide, 2-ethynylpyridine at  $-1.72$  volts, and 2-methyl-5-ethynylpyridine at  $-2.06$  volts (SCE). The reduction potentials of the ethynylpyridines are very close to those of the corresponding vinyl compounds<sup>211</sup>; similar results have been found for benzene derivatives.<sup>212</sup> The electrode reaction would thus be expected to be a four-electron reduction of the ethynyl group to an ethyl group.

## B. HYDROXYL DERIVATIVES

Heterocyclic hydroxyl derivatives can be divided in two groups according to whether the hydroxyl group is exocyclic or not. Heterocyclic compounds having a hydroxyl substituent in the ring have the possibility of existing in different tautomeric forms<sup>213, 214</sup>—the hydroxy or the oxo form—and in many cases the oxo form is

<sup>210</sup> V. D. Bezuglyi and T. A. Alekseeva, *Zh. Anal. Khim.* **20**, 244 (1965).

<sup>211</sup> V. D. Bezuglyi, V. D. Dmitrieva, and T. A. Alekseeva, *Zh. Anal. Khim.* **16**, 477 (1961).

<sup>212</sup> C. Provost, P. Souchay, and J. Chauvelier, *Bull. Soc. Chim. France* 714 (1951).

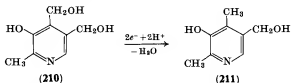
<sup>213</sup> A. R. Katritzky and J. M. Lagowski, *Advan. Heterocycl. Chem.* **1**, Chapters 6 and 7 (1963).

<sup>214</sup> A. R. Katritzky and J. M. Lagowski, *Advan. Heterocycl. Chem.* **2**, Chapters 1 and 2 (1963).

the predominant one. Nevertheless, regardless of the position of the prototropic equilibria the compounds will be treated here as "hydroxyl compounds."

### 1. *Hydroxyl Compounds Attached to a Substituent*

Hydroxyl groups are reducible only when they are activated by an electron-attracting group, e.g., the phenacyl group.<sup>215, 216</sup> A pyridine ring activates its substituents, but particularly so in the 2- and 4-positions. This is illustrated by the reduction of pyridoxol (**210**) which is reducible in an ammoniacal buffer (pH 8.5–10) according to the following reaction<sup>217</sup> where only one of the hydroxyl groups is reductively removed thus forming (**211**).



If the alcohol group is further removed from the ring, the activating influence from the ring is insignificant.

### 2. *Hydroxyl Compounds Attached to the Ring*

a. *Derivatives of Pyrrole.* Succinimide (2,5-dihydroxypyrrole) is not reducible polarographically, but can in the same manner as aliphatic amides be reduced in sulfuric acid at high current densities with simultaneous reduction of some hydrogen ions. High current density and specific adsorption of the substrate to the electrode is important to obtain a reasonable current yield (A2 reaction in Section II, A). At a lead cathode succinimide is reduced to pyrrolidone,<sup>218</sup> whereas some pyrrolidine is formed at an amalgamated zinc electrode.<sup>219</sup>

b. *Derivatives of isoindole.* Phthalimide (**212**) is polarographically

<sup>215</sup> P. Kabasakalian and J. McGlotten, *Anal. Chem.* **31**, 1091 (1959).

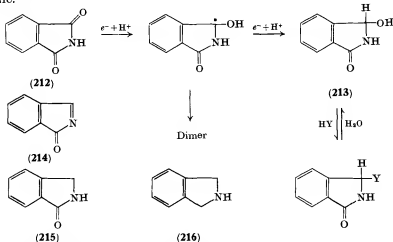
<sup>216</sup> H. Lund, *Acta Chem. Scand.* **14**, 1927 (1960).

<sup>217</sup> O. Manousek and P. Zuman, *Collection Czech. Chem. Commun.* **29**, 1432 (1964).

<sup>218</sup> J. Tafel and M. Stern, *Ber.* **33**, 2224 (1900).

<sup>219</sup> B. Sakurai, *Bull. Chem. Soc. Japan* **10**, 311 (1935).

reduced in acid solution by a two-electron reduction, whereas 2 one-electron waves are found in slightly alkaline medium.<sup>220, 221</sup> The two-electron reduction product,<sup>222</sup> hydroxyphthalimidine (**213**), a derivative of phthalaldehydic acid, reacts with any nucleophile HY present; in ethanolic solution ethoxyphthalimidine is formed and in the presence of isoindoline it gives 1-*N*-isoindolino-3-oxo-isoindoline.<sup>222</sup>



In strongly acid solution **213** is dehydrated to the easily reducible 3-oxoisoindole (**214**) which is reduced to phthalimidine (**215**); a further reduction to isoindoline (**216**) may take place under conditions similar to those used for the reduction of benzamides.<sup>223-225</sup>

The reduction of *N*-anilinophthalimides has been discussed above (Section IV, C).<sup>100</sup>

Hydroxyisoindolines (**217**) are polarographically reducible<sup>226</sup> as would be expected because they are derivatives of an aromatic aldehyde. As other hydrated derivatives of carbonyl or azomethine compounds they must lose water before electrons can be accepted; the reduction proceeds through a radical.

<sup>220</sup> J. Tirouflet, M. Rolin, and M. Guyard, *Bull. Soc. Chim. France* 568 (1956).

<sup>221</sup> A. Ryvolva, *Collection Czech. Chem. Commun.* **25**, 420 (1960).

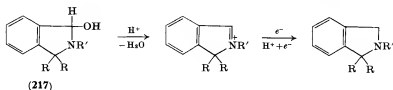
<sup>222</sup> A. Dunet and A. Willemart, *Bull. Soc. Chim. France* 887 (1948).

<sup>223</sup> E. Späth and F. Brench, *Monatsh.* **50**, 349 (1928).

<sup>224</sup> B. Sakurai, *Bull. Chem. Soc. Japan* **5**, 184 (1930).

<sup>225</sup> F. Fichter and I. Stein, *Helv. Chim. Acta* **12**, 821 (1929).

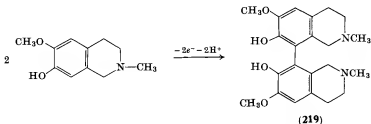
<sup>226</sup> N. P. Shimanskaya, L. A. Pavlova, and V. D. Bezuglyi, *Zh. Obshch. Khim.* **37**, 974 (1967).



c. *Naphthostyryl*. Naphthostyryl (**218**) has been reported to be reduced polarographically<sup>227</sup> at pH 5 in a four-electron reaction, whereas only a two-electron reaction is found at pH 10. The electrode reactions have not been proved yet.



d. *Derivatives of Isoquinoline*. If the hydroxyl group is in the benzene ring of a fused heterocyclic compound, oxidative phenolic coupling reactions may occur.<sup>228, 229</sup> Thus, corypalline (**218a**) yields 28% of the dimer (**219**) on anodic electrolysis in alkaline solution. The same product could be obtained by irradiation of **218a** in aqueous alkali.



e. *Derivatives of Pyridazine*. In both 3-pyridazinones<sup>159, 230</sup> (**220**) and maleic hydrazide (3-hydroxypyridazin-6-one)<sup>231</sup> the first step is

<sup>227</sup> P. M. Zaitsev, Z. V. Zaitseva, and M. A. Mostoslavskii, *Ukr. Khim. Zh.* **34**, 1003 (1968); *Chem. Abstr.* **70**, 53407 (1969).

<sup>228</sup> J. M. Bobbitt, J. T. Stock, A. Marchand, and K. H. Weisgraber, *Chem. Ind. (London)* 2127 (1966).

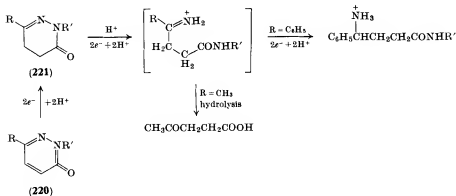
<sup>229</sup> G. F. Kirkbright, J. T. Stock, R. D. Pugliese, and J. M. Bobbitt, *J. Electrochem. Soc.* **116**, 219 (1969).

<sup>230</sup> P. Pfügel, G. Wagner, and O. Manousek, *Z. Chem.* **6**, 263 (1966).

<sup>231</sup> D. H. Miller, *Can. J. Chem.* **33**, 1806 (1955).



saturation of the 4,5-double bond. The further reduction of **221** depends on the substituents in the 6-position; in acid solution 4,5-dihydro-6-phenylpyridazin-3-one (**221**,  $R = C_6H_5$ ) is reduced in a four-electron reaction, whereas 4,5-dihydro-6-methylpyridazin-3-one (**221**,  $R = CH_3$ ) consumes only two electrons per molecule. The reduction of **221** is analogous to the reduction of hydrazones; only the protonated molecule is reducible and the reaction starts with hydrogenation of the nitrogen-nitrogen bond (Scheme 23).



SCHEME 23

When  $R = CH_3$ , the imine is not reducible at the potential necessary for the cleavage of the N-N bond, whereas with  $R = C_6H_5$  the imine, a derivative of propiophenone imine, is further reduced. In some cases ring closure to a pyrrolidone might occur.

Reduction of pyridazin-4-ones seems not to have been reported.

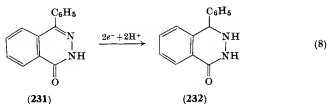
f. *Derivatives of Cinnoline.* 3-Hydroxycinnoline (**222**)<sup>44</sup> is reduced in a two-electron wave from pH 0 to 11. In strongly acid solution the main product is 1-aminooxindole (**223**), which is also obtained on reduction with zinc and sulfuric acid.<sup>232</sup> Reduction in an emulsion of an aqueous phosphate buffer (pH 6.5) and *n*-butanol produced a nearly quantitative yield of 3-keto-1,2,3,4-tetrahydrocinnoline (**224**); this compound was easily reoxidized to 3-hydroxycinnoline.

By choosing a pH for the reduction at which the product is stable, the preparation of this labile compound could be accomplished.

<sup>232</sup> H. E. Baumgarten, P. L. Creger, and R. L. Zey, *J. Am. Chem. Soc.* **82**, 3977 (1960).



g. *Derivatives of Phthalazine.* 1(2*H*)-Phthalazinones (**231**)<sup>40, 233</sup> are reduced in a two-electron reaction to the corresponding 3,4-dihydro-1(2*H*)-phthalazinones (**232**) in neutral and alkaline solution. In mineral acid the reduction products from alkyl phthalazinones can be reduced further in a two-electron reaction with cleavage of the nitrogen–nitrogen bond and ring closure to phthalimidines. The reaction for 4-methyl-1(2*H*)-phthalazinone (**89**) has been discussed (Section IV, B); for 4-phenyl-1(2*H*)-phthalazinone (**231**), see Eq. (8).



The reduction of phthalazinones is apparently the only observed example of a reduction of a protonated compound containing  $>C=N-N<$  in which the  $C=N$  double bond proves to be easier to reduce than the  $N-N$  bond. The differences in reduction potential between the azomethine double bond and the nitrogen–nitrogen bond are not great in acyclic compounds and the presence of a phenyl group fused to the heterocyclic ring may alter several parameters. The phenyl group acts as a nonreducible, nondisplaceable unsaturated center, and its presence may influence the orientation of the molecule and the adsorption of the compound at the electrode.

Dihydroxyphthalazines<sup>40</sup> such as 2,3-dihydro-2,3-dimethyl-1,4-phthalazinedione are reduced at low pH to a phthalimidine in a six-electron reduction; in alkaline solution 4-hydroxy-3,4-dihydro-2,3-dimethyl-1-phthalazinone is formed in a two-electron reaction. In this medium it is not further reducible, but in acid solution it loses water to the reducible phthalazinonium compound. The product from this reaction is 3,4-dihydro-2,3-dimethyl-1-phthalazinone, which at low pH can be reduced to *N*-methylphthalimidine and its precursor *N*-methyl-2-(methylaminomethyl)benzamide. The reduction scheme was given in Section II, D (Scheme 1).

The anodic oxidation of phthalhydrazide and some of its derivatives has been investigated using different electroanalytical techniques<sup>234</sup>

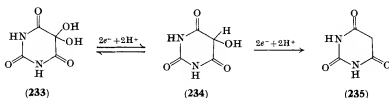
<sup>233</sup> P. Pfügel and G. Wagner, *Pharmazie* **22**, 147 (1967).

<sup>234</sup> B. Epstein and T. Kuwana, *J. Electroanal. Chem.* **15**, 389 (1967).

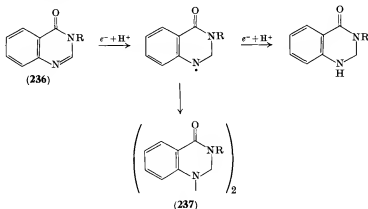
and the oxidation has been shown to be irreversible; the electrode process is, however, not known.

h. *Derivatives of Pyrimidine.* Cytosine is a pyrimidin-2-one, but as the primary reaction involves the amino group it will be treated below (Section VI, E).

Alloxan (233)<sup>235</sup> gives in acid solution a kinetically controlled polarographic wave; the rate-controlling process involved may be the dehydration of the hydrated carbonyl at C-5. The reduction product, dialuric acid (234), can be anodic reoxidized to alloxan or, between pH 4.6 and 6.6, reduced further, probably to barbituric acid (235).



4-Hydroxyquinazoline (236,  $R = H$ )<sup>159, 236, 237</sup> is reducible in neutral and weakly alkaline solution; in strongly alkaline solution the anion is not reducible. The reduction is analogous to the reduction of dihydroquinazoline to tetrahydroquinazoline; at higher concentrations a product dimerized at N-1 (237) was also isolated.<sup>236</sup>



<sup>235</sup> W. A. Struck and P. J. Elving, *J. Am. Chem. Soc.* **86**, 1229 (1964).

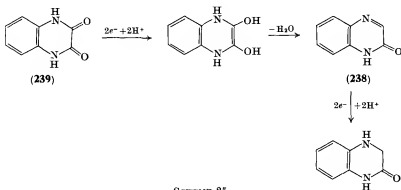
<sup>236</sup> P. Pffegle and G. Wagner, *Pharmazie* **22**, 60, 643 (1967).

<sup>237</sup> P. Pffegle and G. Wagner, *Z. Chem.* **9**, 151 (1969).

The reduction of hypoxanthine<sup>238</sup> follows the same pattern as that of 4-hydroxyquinazoline; generally it is found that reductions in the purine and quinazoline series run parallel.

i. *Derivatives of Quinoxaline.* Both 2-hydroxy- and 2,3-dihydroxyquinoxaline are polarographically reducible, the former by a two-electron reduction and the latter in acid solution by a four-electron reduction.<sup>239</sup> The former is easier to reduce than the latter, which is understandable as 2-hydroxyquinoxaline (**238**) may be regarded as a derivative of glyoxalic acid, whereas 2,3-dihydroxyquinoxaline (**239**) is a derivative of oxalic acid. Derivatives of aldehydes are easier to reduce than the corresponding acid derivatives.

The reduction of 2,3-dihydroxyquinoxaline in acid solution may be formulated as in Scheme 25.



SCHEME 25

Reduction of 3-alkylated 2-hydroxyquinoxalines produces, besides the 3,4-dihydroquinoxalone, a product dimerized at N-4, whereas 3-aryl quinoxalones form only the 3,4-dihydro derivative on reduction.<sup>240</sup>

2,3-Dimethyl-5,8-quinoxalinedione gives two reversible polarographic waves at 0.06 and 0.76 volt (SCE), at pH 7. The first wave corresponds to a reduction of the *p*-quinone system to 2,3-dimethyl-5,8-dihydroxyquinoxaline, whereas the second reduction takes place in the heterocyclic ring and leads to the 1,4-dihydroquinoxaline.<sup>241</sup>

<sup>238</sup> D. L. Smith and P. J. Elving, *J. Am. Chem. Soc.* **84**, 1412 (1962).

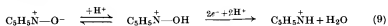
<sup>239</sup> C. Furlani, *Gazz. Chim. Ital.* **85**, 1646 (1955).

<sup>240</sup> P. Pfeffel and G. Wagner, *Z. Chem.* **8**, 179 (1968).

<sup>241</sup> W. F. Gum and M. M. Joullie, *J. Org. Chem.* **32**, 53 (1967).

3. *N*-Oxides

*N*-Oxides of heteroaromatic compounds are generally electrolytically reducible in acid solution<sup>242-254</sup>; the most studied compounds of this type are the pyridine *N*-oxides.<sup>242, 249, 250</sup> At low pH pyridine *N*-oxide gives a two-electron polarographic wave, but at pH > 4 the wave height diminishes, as the preprotonation step becomes too slow [Eq. (9)].



The assumption that it is the *O*-protonated *N*-oxide which is reduced is substantiated by the similarity in reduction potential between pyridine *N*-oxide and *N*-methoxypyridinium ion in acid solution; the latter is also reducible in alkaline solution.<sup>94</sup>

A number of different *N*-oxides have been investigated polarographically, such as the *N*-oxides of quinoline,<sup>252</sup> acridine,<sup>244</sup> pyrazine,<sup>254</sup> quinoxaline,<sup>243</sup> phenazine,<sup>246</sup> and adenine,<sup>248</sup> and the influence of substituents has been discussed.

When the heterocyclic ring contains more than one nitrogen atom, the initial reduction of the *N*-oxide may take place in the nucleus, or the reduction of the nucleus and the *N*-oxide function occurs simultaneously. The reduction of quinazoline-3-oxide,<sup>166</sup> 3-methoxy-2,5-

<sup>242</sup> E. Ochiai, *J. Org. Chem.* **18**, 534 (1953).

<sup>243</sup> A. Foffani and F. Fornasari, *Gazz. Chim. Ital.* **83**, 1051, 1059 (1959).

<sup>244</sup> L. V. Varyukhina and Z. V. Pushkareva, *Zh. Obshch. Khim.* **26**, 1740 (1956); *Chem. Abstr.* **51**, 1960 (1957).

<sup>245</sup> O. N. Nechaeva and Z. V. Pushkareva, *Zh. Obshch. Khim.* **28**, 2693 (1958); *Chem. Abstr.* **53**, 9229 (1959).

<sup>246</sup> T. R. Emerson and C. W. Rees, *J. Chem. Soc.* 1923 (1962).

<sup>247</sup> N. A. Kudryavtseva, Z. V. Pushkareva, and V. F. Gryazev, *Zh. Obshch. Khim.* **35**, 14 (1965).

<sup>248</sup> C. R. Warner and P. J. Elving, *Collection Czech. Chem. Commun.* **30**, 4210 (1965).

<sup>249</sup> T. Kubota and H. Miyazaki, *Bull. Chem. Soc. Japan* **35**, 1549 (1962).

<sup>250</sup> T. Kubota and H. Miyazaki, *Bull. Chem. Soc. Japan* **39**, 2057 (1966).

<sup>251</sup> I. Suzuki, M. Nakadate, T. Nakashima, and N. Nagasawa, *Tetrahedron Letters* 2899 (1966).

<sup>252</sup> M. Tachibana, S. Sawaki, and Y. Kawazoe, *Chem. Pharm. Bull.* **15**, 1112 (1967).

<sup>253</sup> J. Hranilovic, D. Koruncev, and E. Gustak, *Electrochem. Tech.* **6**, 62 (1968).

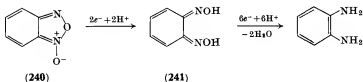
<sup>254</sup> T. Okano and K. Ohira, *Yakugaku Zasshi* **88**, 1170 (1968); *Chem. Abstr.* **70**, 16609 (1969).

dimethylpyrazine-1-oxide,<sup>254</sup> and cinnoline mono- and dioxide<sup>251</sup> is reported to take this route. This might be the reason why *N*-oxidation of the second nitrogen in diazaheterocycles has very little influence on the half-wave potential.

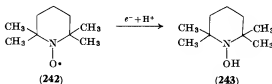
At pH < 1.5, however, *N*-oxides such as those of cinnoline,<sup>44</sup> 3,6-diphenylpyridazine,<sup>94</sup> and pyrazine,<sup>254</sup> give a two-electron polarographic wave followed by the reduction waves of the parent compounds. An attempt based on this to reduce a benzo-1,2,3-triazine-3-oxide to the parent compound failed as the compound was hydrolyzed too rapidly in strongly acid solution.

The initial reduction of 4-nitropyridine-1-oxide<sup>250</sup> takes place in the nitro group which is reduced to the hydroxylamino group; the reduction potentials of the hydroxylamino and the *N*-oxide function are, however, rather close, so it would be difficult to reduce one group without touching the other. In the reduction of 4-nitroquinoline-1-oxide the polarographic evidence suggests that the second wave is caused by reduction of the hydroxylamino group to the amine, whereas the third wave is due to the removal of the *N*-oxide function.<sup>252</sup>

A special type of reduction is exhibited by the benzofuroxans (**240**); these are generally reduced<sup>186, 255</sup> in two or three steps. The first two-electron reduction results in ring opening to an *o*-quinone dioxime (**241**) which is further reduced at a more negative potential.



The stable free radical, the *N*-oxide of 2,2,6,6-tetramethylpiperidine (**242**), is irreversibly reduced at the dropping mercury electrode in a one-electron reaction to the hydroxylamine (**243**).<sup>256</sup>







The hydration is most pronounced when the formyl group is in a position strongly activated toward nucleophilic attack; thus, 2- and 4-formylpyridine are hydrated more than the 3-isomer, 2-formylimidazole<sup>263</sup> and 2-formylthiazole<sup>264</sup> more than the 4- and 5-isomers. The quaternary derivatives are hydrated at least as strongly as the protonated parent compounds and over a wider pH range.

The electrode reaction is over the greater part of the pH region a two-electron reduction to the alcohol, but in strongly alkaline solution an appreciable amount of pinacol is formed. The stereochemistry of the pinacol mixture has not yet been investigated.

The corresponding methyl hetaryl ketones are much less hydrated,<sup>265, 266</sup> as would be expected, and their electrochemical behavior resembles more that of acetophenone. Depending on pH, the products are the pinacols, the carbinol, or mixtures thereof<sup>267-269</sup>; in acid solution mostly carbinols, at high pH mostly pinacols, are formed. The proportion of  $\pm$ -pinacol to *meso*-pinacol obtained in the electrolytic reduction of 2-acetopyridine is, however, different from that from acetophenone.<sup>268, 269</sup> The  $\pm$ /*meso* ratio in alkaline solution is about 2.8 for acetophenone and about 0.3 for 2-acetopyridine.

The pinacols of acetophenones are formed by coupling of two radicals or—in alkaline solution—a radical and a radical anion. It has been proposed that the  $\pm$ /*meso* ratio is determined partly by steric factors, which favors the *meso* form, and partly by hydrogen bonding in the transition state, which favors the  $\pm$ -form. The one-electron reduction product from 2-acetopyridine can exist as the protonated radical, the uncharged radical, and the radical anion. Due to internal hydrogen bonding in the radical the importance of hydrogen bonding between the two radicals approaching each other in the transition state is diminished and the relative importance of the steric factors is enhanced, which leads to a lower  $\pm$ /*meso* ratio<sup>268, 269</sup> compared with that found in the reduction of acetophenone.

<sup>263</sup> P. E. Iversen and H. Lund, *Acta Chem. Scand.* **21**, 279 (1967).

<sup>264</sup> J. Tirouflet, E. Laviron, J. Metzger, and J. Boichard, *Collection Czech Chem. Commun.* **25**, 3277 (1960).

<sup>265</sup> J. Volke, *Collection Czech. Chem. Commun.* **25**, 3397 (1960).

<sup>266</sup> E. Laviron, *Bull. Soc. Chim. France* 418 (1962).

<sup>267</sup> M. J. Allen, *J. Org. Chem.* **15**, 435 (1950).

<sup>268</sup> J. H. Stocker and R. M. Jenevein, *J. Org. Chem.* **33**, 294 (1968).

<sup>269</sup> J. H. Stocker and R. M. Jenevein, *Symp. Synthetic Mechanistic Aspects Electro-org. Chem., Durham, North Carolina, 1968, Preprints of Papers p. 221; J. Org. Chem.* **34**, 2807, 2810 (1969).

Sometimes the polarographic behavior of heteroaromatic compounds is complicated by adsorption of depolarizer and/or products; the adsorbability generally increases with the number of aromatic nuclei in the molecule. In the reduction of benzoyl pyridines<sup>270</sup> it was found that the adsorption of both depolarizer and products was important in acid solution, whereas only the former was adsorbed at high pH.

Formyl derivatives of diazaheteroaromatic compounds would be expected to be hydrated, but in this case the nucleus would also be reducible; carbonyl derivatives of  $\pi$ -electron-rich heterocyclic compounds would be expected to behave pretty much as the corresponding benzene derivatives.

The electrochemical behavior of azomethine derivatives, e.g., oximes, of heteroaromatic carbonyl compounds is much like that of the corresponding benzene derivatives.<sup>91</sup> Pyridine aldoximes<sup>271-274</sup> and ketoximes<sup>275</sup> are reduced in acid solution by a four-electron reaction to the amine. The reaction mechanism is probably, as in other oximes,<sup>91</sup> a reduction of the protonated compound with cleavage of the N-O bond, followed by saturation of the C=N double bond. The amine is often further reducible at a more negative potential (Section VI, E).

An azomethine derivative is generally more easily reducible than the parent carbonyl compound and this can be exploited in cases where the equilibrium between the carbonyl compound and the azomethine derivative favors the former. By reduction at a potential at which the azomethine derivative, but not the carbonyl compound, is reduced, the azomethine is continuously removed from the equilibrium by reduction to amine as it is formed.<sup>91</sup> This technique has been used for the preparation of 2-anilinomethylthiazole.<sup>276</sup>

Anodic oxidation at a mercury anode of aldehydes is possible in alkaline solution; pyridine-4-carbaldehyde was thus found to give

<sup>270</sup> J. Volke and M. M. Amer, *Collection Czech. Chem. Commun.* **29**, 2134 (1964).

<sup>271</sup> J. Volke, R. Kubicek, and F. Santavy, *Collection Czech. Chem. Commun.* **25**, 871 (1960).

<sup>272</sup> O. Manousek, *Collection Czech. Chem. Commun.* **25**, 2250 (1960).

<sup>273</sup> M. Matsumoto, M. Miyazaki, and M. Ishii, *Yakugaku Zasshi* **88**, 1083 (1968); *Chem. Abstr.* **70**, 16525 (1969).

<sup>274</sup> N. G. Lordi and E. M. Cohen, *Anal. Chim. Acta* **25**, 281 (1961).

<sup>275</sup> L. W. Harrison and G. E. Cheney, *Talanta* **15**, 1413 (1968).

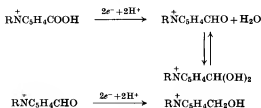
<sup>276</sup> P. E. Iversen and H. Lund, Unpublished results.

an anodic wave due to an oxidation to isonicotinic acid.<sup>277</sup> Other aldehydes behave similarly.<sup>278</sup>

#### D. CARBOXYLIC ACIDS AND DERIVATIVES

Carboxylic acids and most of their derivatives are difficult to reduce, and polarographic reduction of a carboxyl group requires activation by a strongly electron-attracting group; the addition of electrons may take place either to the carboxyl group or to the activating group, often depending on pH.

$\pi$ -Electron-deficient heterocyclic nuclei may activate a carboxyl group sufficiently to render it polarographically reducible<sup>263, 279-282</sup>; an aldehyde is always easier to reduce than the corresponding carboxylic acid so it is generally not possible to isolate aldehydes from reduction of acids. However, the groups which activate a carboxyl group toward reduction also activate the aldehyde toward nucleophilic addition reactions, and these aldehydes are in a certain pH region hydrated to a certain degree. It is thus possible in some cases to trap the aldehyde as the nonreducible hydrate. As some of the free aldehyde is always present in equilibrium with the hydrate, the reduction of an acid to an aldehyde must be performed at a suitable pH and at a low temperature, where the rate of the dehydration reaction is low. The reduction must not be allowed to proceed to completion, but must be stopped after the consumption of about two electrons per molecule. The reaction may be formulated as shown in Scheme 27.



SCHEME 27

<sup>277</sup> H. Lund, *Acta Chem. Scand.* **17**, 1077 (1963).

<sup>278</sup> J. Volke, *J. Electroanal. Chem.* **10**, 344 (1965).

<sup>279</sup> J. Volke and V. Volkova, *Collection Czech. Chem. Commun.* **20**, 1332 (1955).

<sup>280</sup> H. H. G. Jellinek and J. R. Urwin, *J. Phys. Chem.* **58**, 168 (1954).

<sup>281</sup> H. Lund, *Acta Chem. Scand.* **17**, 972 (1963).

<sup>282</sup> P. E. Iversen and H. Lund, *Acta Chem. Scand.* **21**, 389 (1967).

In acid solution the carbinol might be reduced further. Pyridine carboxylic acids,<sup>281</sup> 2-carboxythiazoles,<sup>282</sup> and 2-carboxyimidazoles<sup>283</sup> and their amide derivatives have been reduced in this way. The yields of aldehydes in some of these reactions are given in Table I.<sup>283</sup>

TABLE I

YIELDS OF ALDEHYDES FROM ELECTROLYTIC REDUCTION OF HETEROAROMATIC CARBOXYLIC ACID DERIVATIVES<sup>a</sup>

Starting material	Yield (%)	
	Analysis	Isolated
2-Pyridinecarboxamide	72.5	53.5
4-Pyridinecarboxamide	57	49
2-Thiazolecarboxamide	81.5	44
4-Methyl-2-thiazolecarboxamide	82.5	52.5
<i>N</i> -Benzyl-2-carboxyimidazole	89	77
<i>N</i> -Methyl-2-carboxyimidazole	71	59
2-Carboxyimidazole	83.5	60

<sup>a</sup> In acid medium at 15°C on a 0.2 mole scale at a mercury cathode.

When the reduction is performed without control of the potential, a mixture of products results. Thus, reduction in sulfuric acid at lead or mercury cathodes of the pyridine carboxylic acids leads to a mixture of picolines and tetra- and hexahydropyridine derivatives.<sup>284-287</sup> Derivatives of nicotinic acid are more apt to be reduced in the ring than the 2- and 4-carboxypyridines. Reduction of the corresponding pyridylcarbinols under identical conditions produces a similar reaction mixture.<sup>287</sup>

The polarographic wave height of 2,3- and 3,4-dicarboxypyridine points to a two-electron reduction.<sup>288</sup> It is not known whether the reduction results in formation of a hydrated aldehyde or in a dihydropyridine; the latter reaction probably occurs in alkaline solution.

<sup>283</sup> P. E. Iversen, *Acta Chem. Scand.* **24** (1970) in press.

<sup>284</sup> F. Šorm, *Collection Czech. Chem. Commun.* **13**, 57 (1948).

<sup>285</sup> J. P. Wibaut and H. Boer, *Rec. Trav. Chim.* **68**, 72 (1949).

<sup>286</sup> M. Ferles and M. Prystaš, *Collection Czech. Chem. Commun.* **24**, 3326 (1959).

<sup>287</sup> M. Ferles and A. Tesařová, *Collection Czech. Chem. Commun.* **32**, 1631 (1967).

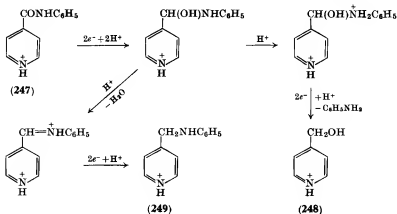
<sup>288</sup> J. Volke, *Collection Czech. Chem. Commun.* **22**, 1777 (1957).

3-Carboxypyridazine is reduced in the ring and a similar reduction would be expected for carboxy derivatives of other diazaheterocyclic compounds.

a. *Anodic reactions.* Kolbe reactions of heterocyclic compounds have been studied only in a few cases. Anodic oxidation of 1-azabicyclo[2.2.2]octane-2-carboxylic acid (**244**) under "Kolbe conditions" produced 2-methoxy-1-azabicyclo[2.2.2]octane (**245**).<sup>289</sup> The primary radical, formed by loss of an electron from the carboxylate ion, is decarboxylated and oxidized further to the carbonium ion (**246**) which is attacked by a methoxide ion.



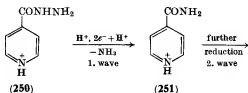
b. *Esters, Amides, Thiamides, and Hydrazides.* The reduction of esters and amides follows a similar route as that of the parent acids. Thus, ethyl isonicotinate and isonicotinic amides<sup>127</sup> are reduced in acid solution through the aldehyde, which can be isolated in a higher yield than from the acid. From the reduction of isonicotinic anilide (**247**) it was not possible to isolate any aldehyde; the reduction yielded a mixture of the 4-pyridylcarbinol (**248**) and 4-anilinomethylpyridine



<sup>289</sup> P. G. Gassman and B. L. Fox, *J. Org. Chem.* **32**, 480 (1967).

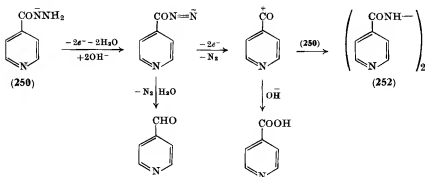
(249).<sup>127</sup> Similar results have been obtained in the thiazole<sup>282</sup> and imidazole series.<sup>263</sup>

c. *Hydrazides*. A hydrazide such as isonicotinic hydrazide (250)<sup>290</sup> shows both cathodic and anodic polarographic waves. The electrode reaction of the first cathodic wave in acid solution was found to be cleavage of the nitrogen–nitrogen bond and the second one the reduction of the amide (251) thus formed; this reduction has been discussed above.



In alkaline solution reduction takes place in the nucleus.

The height of the anodic wave in alkaline solution corresponds to a four-electron reaction, but a preparative oxidation at pH 11 (phosphate buffer) produced 1,2-diisonicotinoylhydrazine (252) by a two-electron reaction. At pH 13 the oxidation required 2.9 electrons per molecule and about 45% isonicotinic acid and 55% 252 was formed. The reaction has been formulated as Scheme 28.



SCHEME 28

d. *Nitriles*. Anodic cyanidation of pyridine to 2-cyanopyridine has been reported<sup>291</sup>; as anodic substitution occurs most readily in easily

<sup>290</sup> H. Lund, *Acta Chem. Scand.* **17**, 1077 (1963).

<sup>291</sup> S. Andreades, U.S. Patent 3431 184 (1969); *Chem. Abstr.* **70**, 92678 (1969).

oxidized compounds and as pyridine is very difficult to oxidize, the yield would not be expected to be high.

The reduction of 2- and 4-cyanopyridine (**253**) exhibits special features (Fig. 10). In acid solution the protonated species is reduced in

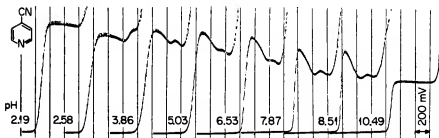
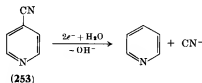


Fig. 10. Polarographic curves of 4-cyanopyridine. The curves start at  $-0.2$  volt (SCE); 200 mvolt/mark. From Volke and Holubek.<sup>293</sup>

a four-electron reaction<sup>292-294</sup> to the pyridylmethylamine, but in alkaline medium the carbon-carbon bond was cleaved with formation of pyridine and cyanide ion.<sup>127, 293</sup>



The stability of the cyanide ion is important in this reductive cleavage; benzonitriles bearing strongly electron-attracting groups may be reduced similarly in basic media.<sup>295</sup>

The change in electrode reaction takes place between pH 5 and 8, and it was found that at a given pH in this region the course of the reaction depended on the electrode potential. The two-electron cleavage was favored at more negative potentials.<sup>30</sup> The phenomenon may result from a potential-dependent orientation of **253** at the surface of the electrode<sup>30</sup> or from a potential-dependent branching of the reaction.

<sup>292</sup> J. Volke, R. Kubicek, and F. Santavy, *Collection Czech. Chem. Commun.* **25**, 1510 (1960).

<sup>293</sup> J. Volke and J. Holubek, *Collection Czech. Chem. Commun.* **28**, 1597 (1963).

<sup>294</sup> E. Laviron, *Compt. Rend.* **250**, 3671 (1960).

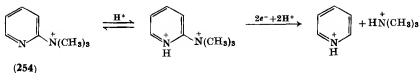
<sup>295</sup> O. Manousek, P. Zuman, and O. Exner, *Collection Czech. Chem. Commun.* **33**, 3979 (1968).

## E. NITROGEN-CONTAINING SUBSTITUENTS

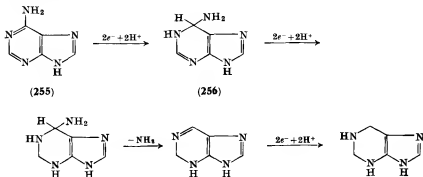
In this section the electrode reactions of amines and nitro and nitroso compounds will be discussed. The presence of an amino group usually makes the reduction of a molecule more difficult, but the amino group is, in most cases, not directly involved in the reduction. Three types of exception have been found.

*N*-Aminopyridinium iodide is reduced in acid solution to pyridine; similar *N*-amino heteroaromatics are probably reduced in the same way.<sup>94</sup>

Activated amino groups, such as those found in 4-pyridylmethylamines<sup>296</sup> or 2-pyridyltrimethylammonium iodide (254),<sup>94</sup> are reductively removed in acid solution. The reduction of the latter requires protonation of the ring to obtain sufficient activation.



Elimination of an amino group is sometimes found as a chemical step between the transfer of electrons. The reduction of adenine (255) illustrates this.<sup>297</sup>



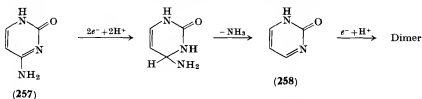
An elimination of ammonia from 256 to purine followed by reduction of this compound is also possible.

<sup>296</sup> O. Manousek and P. Zuman, *Collection Czech. Chem. Commun.* **29**, 1432 (1964).

<sup>297</sup> D. L. Smith and P. J. Elving, *J. Am. Chem. Soc.* **84**, 1412 (1962).

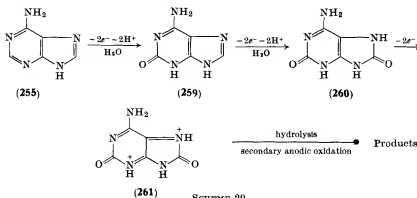


Cytosine (**257**) loses ammonia in a two-electron reduction<sup>298</sup> with the formation of 2-pyrimidone (**258**), which, as other pyrimidones,<sup>299</sup> is reduced in a one-electron reaction with dimerization.



The anodic oxidation of 2,5- and 4,5-diaminopyrimidines has been investigated using a rotating platinum electrode, but the electrode reactions are not known.<sup>300</sup>

Adenine (**255**) gives a single well-defined voltammetric wave at the pyrolytic graphite microelectrode<sup>301</sup>; coulometric data showed a six-electron oxidation. Exhaustive electrolysis at a fixed anode potential in aqueous 1 *M* acetic acid solution produced a mixture of products, the reaction starting with an anodic hydroxylation of **255** to **259** and **260** (Scheme 29).



SCHEME 29

The unstable dication (**261**) is hydrolyzed and some products are oxidized further. From the electrolyzed solution, urea, parabanic acid (**262**), oxaluric acid (**263**), ammonia, 4-aminopurpuric acid (**264**), and possibly allantoin (**265**) were isolated.

<sup>298</sup> D. L. Smith and P. J. Elving, *J. Am. Chem. Soc.* **84**, 2741 (1962).

<sup>299</sup> G. K. Budnikov, *Zh. Obshch. Khim.* **38**, 2431 (1968).

<sup>300</sup> D. Cohen, M. Koenigsbuch, and M. Sprecher, *Israel J. Chem.* **6**, 615 (1968).

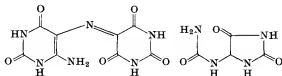
<sup>301</sup> G. Dryhurst and P. J. Elving, *J. Electrochem. Soc.* **115**, 1014 (1968).



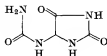
(262)



(263)



(264)



(265)

*N*-Nitroso derivatives of saturated heterocycles, such as *N*-nitrosopiperidine, behave polarographically as their open-chain analogs.<sup>302-305</sup> The reduction in acid solution is a four-electron reduction to the hydrazine, whereas the two-electron reduction found in alkaline media is a cleavage of the N-N bond.<sup>303</sup>

The corresponding *N*-nitro derivatives behave similarly<sup>306-308</sup>; in acid solution the hydrazines are produced in a six-electron reaction, in alkaline medium the first two-electron reduction results in the formation of the *N*-nitroso derivatives which at a more negative potential are further reduced. *N*-Nitropyrzole behaves slightly differently as the reduction in acid solution also results in a cleavage of the N-N bond with formation of nitrous acid. 2-Nitraminopyridine<sup>309</sup> in acid solution is reduced to the hydrazine. In alkaline solution the anion is reducible, in contradistinction to most nitramines derived from primary amines. The four-electron reduction yields 2-aminopyridine. Pyridine 1-nitroimide is reduced to pyridine.<sup>309</sup>

*C*-Nitro derivatives of heteroaromatic compounds behave polaro-

<sup>302</sup> F. L. English, *Anal. Chem.* **23**, 344 (1951).

<sup>303</sup> H. Lund, *Acta Chem. Scand.* **11**, 990 (1957).

<sup>304</sup> R. Zahradník, *Chem. Listy* **51**, 937 (1957).

<sup>305</sup> E. A. M. Dahmen, D. Vader, and J. D. van der Laarse, *Z. Anal. Chem.* **186**, 161 (1962).

<sup>306</sup> E. Laviron and P. Fournari, *Bull. Soc. Chim. France* 518 (1966).

<sup>307</sup> E. Laviron, P. Fournari, and J. Greusard, *Bull. Soc. Chim. France* 1255 (1967).

<sup>308</sup> E. Laviron, P. Fournari, and G. Refalo, *Bull. Soc. Chim. France* 1024 (1969).

<sup>309</sup> H. Lund, Unpublished observation.

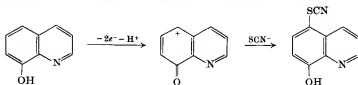
graphically like the corresponding benzene derivatives.<sup>252, 310-312</sup> Thus, in acid solution a four-electron wave is found followed by a two-electron reduction of the hydroxylamine formed in the first reaction. As a hydroxylamine is not reducible in alkaline solution, only the first four-electron wave is observed in this medium.

Electrolysis of such nitro compounds would be expected to conform to the polarographic results in acid solution, but in alkaline medium coupling to azoxy derivatives and further reduction to hydrazo compounds must be expected.

### F. SULFUR-CONTAINING SUBSTITUENTS

Electrolytic introduction of sulfur-containing substituents may be performed by anodic thiocyanation. The primary anodic process of an aromatic system in such a reaction is the loss of an electron with formation of a cation radical. This radical may lose a proton or react with a nucleophile to give a neutral radical which again may lose an electron to form a carbonium ion; loss of a proton or reaction with a nucleophile may complete the reaction.

8-Hydroxyquinoline (266) has been reported to undergo anodic thiocyanation and 8-hydroxy-4-thiocyanatoquinoline has been suggested as the product.<sup>313</sup> It seems, however, much more likely that the substituent is introduced in the 5-position (Scheme 30).



SCHEME 30.

Electron-donating groups facilitate the reaction, which also would be expected to occur much more easily with  $\pi$ -electron-rich hetero-aromatic systems than with  $\pi$ -electron-deficient ones.

Thiocyanate groups may also be introduced by the "cathodic substitution" reaction discussed in Section IV, A,1.

<sup>310</sup> J. Holubek and J. Volke, *Collection Czech. Chem. Commun.* **25**, 3286 (1960).

<sup>311</sup> E. Laviron, *Bull. Soc. Chim. France* 2840 (1963).

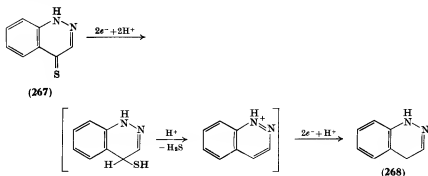
<sup>312</sup> P. C. Jain and R. C. Kapoor, *J. Polarog. Soc.* **14**, 101 (1968).

<sup>313</sup> N. N. Mel'nikov, S. I. Sklyarenko, and E. M. Cherkasova, *Zh. Obshch. Khim.* **9**, 1819 (1939).

Sulfhydryl groups usually make a molecule polarographically active in alkaline solution where the anodic wave is caused by the formation of a mercurous salt. This is, for example, found for the anodic wave of 1-hydroxypyridine-2-thione.<sup>314</sup> In acid medium heteroaromatic mercapto compounds are mostly found on the thio-carbonyl forms. Few of these compounds have been investigated.

Pyrimidinethiones, such as 4,6-dimethyl-2-pyrimidinethione, give a one-electron reduction wave which suggests the formation of a dimerized product.<sup>299</sup>

4-Mercaptocinnoline (267)<sup>44</sup> gives a two-electron polarographic wave, but a preparative reduction consumed four electrons per molecule and produced 1,4-dihydrocinnoline (268). The reaction thus must involve a slow step after the first two-electron reduction and has been formulated as shown, where the slow chemical step in the reaction is the acid-catalyzed elimination of hydrogen sulfide.



A similar reaction may be expected in the reduction of mercapto derivatives of other diazaheteroaromatic compounds.

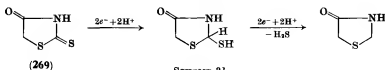
2-Mercapto-4-hydroxythiazole (rhodanine) (269) is reducible in two two-electron steps,<sup>315</sup> the second step being found at rather negative potentials. The reduction takes place at the exocyclic sulfur and has been formulated as shown in Scheme 31.

When 4,4'-dithiodimorpholine was reduced in slightly acidic solution, the products were morpholine and sulfur.<sup>316</sup> If the

<sup>314</sup> A. F. Krivis and E. S. Gazda, *Anal. Chem.* **41**, 212 (1969).

<sup>315</sup> C. Dreux, M.-L. Girard, and P. Souchay, *Compt. Rend.* **262**, 1565 (1966).

<sup>316</sup> H. Lund, *Lecture, 19th Intern. Congr. Pure Appl. Chem., London, 1963*, *Abstr.* p. 466.

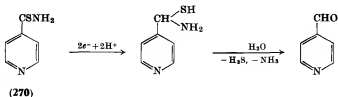


*N*-mercapto derivative is formed primarily on reduction of the disulfide, it must decompose rapidly.

Disulfides are generally reduced without difficulty to the mercapto derivative; 8,8'-diquinolyldisulfide<sup>317</sup> has thus been reported to be reduced in this way. The disulfide group is reduced preferentially to an *N*-oxide function, e.g., bis(2-pyridyl)disulfide-di-*N*-oxide.<sup>318</sup>

The reduction of heterocyclic thiocyanates has not been reported; the reaction would be expected to be a reduction to cyanide ion and a mercapto compound.

Isonicotinic thiamide (270)<sup>127</sup> is reduced as other thiamides<sup>319</sup>; the primary reduction product, the *gem*-aminothiols, R-CH(SH)NH<sub>2</sub>, is fairly stable in cold acidic solution, but decomposes on evaporation of the solvent to hydrogen sulfide and the pyridine-4-carbaldehyde.



## G. HALOGEN DERIVATIVES

Anodic halogenation proceeds usually as the thiocyanation discussed above (Section VI, F), but may also involve the free halogen or a halogen cation. Anodic halogenation may be advantageous in fluorination and iodination reactions, and in halogenations where a low, easily measured concentration of halogen is desirable.

Fluorination of pyridine yields, *inter alia*, perfluoropiperidine.<sup>320</sup> Iodine has been introduced in the 5- and 7-positions of 8-hydroxyquinoline.<sup>321</sup> "Cathodic halogenation" has been mentioned in Section IV, A, 1, b.

<sup>317</sup> J. J. Donahue and J. W. Olver, *Anal. Chem.* **41**, 753 (1969).

<sup>318</sup> I. El-Khiami and R. M. Johnson, *Talanta* **14**, 745 (1967).

<sup>319</sup> H. Lund, *Collection Czech. Chem. Commun.* **25**, 3313 (1960).

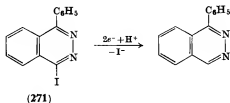
<sup>320</sup> T. C. Simmons and F. W. Hoffmann, *J. Am. Chem. Soc.* **79**, 3429 (1957).

The reducibility of a halogenated heteroaromatic system depends on the heteroaromatic ring, the kind of halogen, and the position of the substituent. Iodides are more easily reducible than bromides which, in turn, are easier than chlorides. Halogen substituents in positions activated toward nucleophilic attack are preferentially reduced.

The electrode reaction may be either a reduction of the carbon-halogen bond or a reduction of the nucleus.

Several heterocyclic halogen derivatives have been investigated polarographically, such as 4-chloro, 2-, 3-, and 4-bromopyridine,<sup>262</sup> 1,4,5-tribromo- and 1,4,5-triiodoimidazole.<sup>311</sup> In some cases further polarographic waves indicate the nature of the product. Thus, the second wave of 4-iodo-1-methylphthalazine is that of 1-methylphthalazine,<sup>159</sup> the polarogram of 1,4,5-triiodoimidazole shows a stepwise removal of the halogens,<sup>311</sup> and the second wave of 4-chloroquinazoline in acid solution is the wave of the unhydrated, protonated quinazoline.<sup>166</sup>

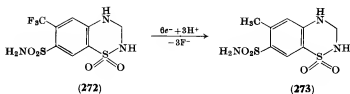
Large-scale reductive removal of halogens is sometimes of preparative value; thus, it is convenient to remove chlorine from 4-chloroquinazoline<sup>166</sup> and iodine from 4-iodophthalazines (271)<sup>169</sup> by reduction at a mercury cathode and chlorine from 2-amino-4-chloropyrimidine at a spongy cadmium electrode.<sup>322</sup> Although the polarograms indicate slightly easier reduction of the C-Cl bond than of the phthalazine nucleus, it has been difficult to remove the chlorine from 4-chlorophthalazine without reducing the nucleus.



3-Chloro-6-methylpyridazine is reduced in a two-electron reaction; the isolated product is 4,5-dihydro-6-methyl-3-pyridazinone. This indicates that the reduction takes place in the ring and the chlorine is then lost by hydrolysis.<sup>159</sup>

<sup>321</sup> O. W. Brown and B. Berkowitz, *Trans. Electrochem. Soc.* **75**, 385 (1939).

<sup>322</sup> K. Sugino, K. Shirai, T. Sekine, and K. Odo, *J. Electrochem. Soc.* **104**, 667 (1957).



6-Trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (**272**) is polarographically active and the product found in a macroscale reduction is the corresponding 6-methyl compound (**273**).<sup>323</sup> The removal of the three fluorine atoms (six electrons) occurs at the same potential and not stepwise as in many polyhalogenated compounds. It is interesting that the reduction at the dropping mercury electrode seems to differ from that at a macroelectrode; a coulometric analysis using the dropping mercury electrode indicated  $n = 4$ , and the corresponding reaction may involve cleavage of the C-S bonds.<sup>324</sup>

<sup>323</sup> H. Lund, *Acta Chem. Scand.* **13**, 192 (1959).

<sup>324</sup> O. Manousek, P. Zuman, and H. Lund, Unpublished observation.

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Numbers in parentheses are reference numbers and indicate that an author's work is referred to although his name is not cited in the text. Numbers in italics show the page on which the complete reference is listed.

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